

Preface

The effect of substituents on benzenoid reactivity has been one of the most extensively investigated branches of chemistry. The scattered data on pyridine substitution are now assembled in a review by R. A. Abramovitch and J. G. Saha which is as valuable for showing what remains to be done as for what has been achieved. R. E. Lyle and P. S. Anderson survey reactions of nitrogen heterocycles with complex hydrides, and the heterocyclic chemistry of nitriles and nitrilium salts is covered by F. Johnson and R. Madroño.

Each of the remaining three chapters deals with a group of compounds: cyclic enamines (K. Bláha and O. Červinka), pyrazoles (A. N. Kost and I. I. Grandberg), and physicochemical aspects of purines (J. H. Lister).

Suggestions are welcome for contributions to further volumes; they should be in the form of a short synopsis.

We thank the Editorial Board, the publishers, and the authors for their cooperation.

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Norwich, England

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Physicochemical Aspects of the Chemistry of Purines

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I. Introduction

The past decade has seen the synthesis of many hundreds of purines and their analogs, the majority of which are the results of research programs whose aim was the production of new chemotherapeutic agents for use against neoplastic diseases. This same period also witnessed the elucidation of the fine details of the basic structure of the nucleic acids in which virtually the whole purine content was found to be composed of adenine and guanine. From these studies, in both the natural and synthetic fields, have emerged much data on the physicochemical nature of these bases. It is the purpose of this review to attempt to show how some of this knowledge may be used to explain some reactions in purine chemistry in fairly general terms of the activated sites and ionization states of the molecules. However, the present state of knowledge is such that all factors concerned in any one reaction may not be fully appreciated and this is seen in the apparent exceptions which are found to the general rules.

Other reviews are available dealing with specialized purine topics, which include their general chemistry,¹ synthesis from pyrimidines² and imidazoles,³ biological synthesis,⁴ and nucleoside chemistry.⁵

¹ G. A. Howard, in "Chemistry of Carbon Compounds" (E. H. Rodd, ed.), Vol. IVc, Chapter 20. Elsevier, Amsterdam, 1960.

² J. H. Lister, *Rev. Pure Appl. Chem.* **11**, 178 (1961).

³ J. H. Lister, *Rev. Pure Appl. Chem.* **13**, 30 (1963).

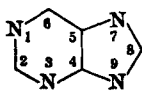
⁴ J. M. Buchanan, *Harvey Lectures* **54**, 104 (1960).

⁵ J. A. Montgomery and H. J. Hewson, *Advan. Carbohydrate Chem.* **17**, 301 (1962).

II. Molecular Structure of Purines

A. ELECTRON DISTRIBUTION

Because of its historical association, the original ring numbering (1) adopted by Fischer⁶ is still used in preference to that of the Ring Index,⁷ standard for purine analogs, which designates purine as 9-(or 7-)-*H*-imidazo(4,5-*d*)pyrimidine.



(1)

In considering the nature of the ring system, the properties of the component parts must be taken into account. For this purpose purine can be assumed to be derived by fusion of a pyrimidine and an imidazole ring such that carbon atoms at the 4- and 5-positions of each ring are common to both. Because of the competition of the two doubly bonded nitrogen atoms for the π -electrons, pyrimidine is an example of a π -electron-deficient system; imidazole, on the other hand, in having both a doubly and singly bonded nitrogen atom, is representative of a π -electron-excessive system. As a consequence, the electron distribution in purine is a result of the two effects, with the pyrimidine ring having a share of the imidazole electrons. One consequence of the partial localization of the electron distribution is the establishment of dipoles which are usually resolved along the long and short axes of the molecule. Purine is claimed⁸ to be long axis major polarized, but the introduction of strong electron-releasing or -withdrawing groups can modify or reverse the direction of the dipole effect. One school⁹ asserts that 9-methyladenine shows its major dipole effect along the short axis, a situation which crystallographic evidence indicates may also exist with 1,3,7,9-tetramethyluric acid, although the related purines, theophylline and caffeine, show long axis major polarization.¹⁰ Theoretical treatment, using Pariser-Parr self-

⁶ E. Fischer, *Ber. Deut. Chem. Ges.* **30**, 557 (1897).

⁷ "The Ring Index," 2nd ed. Am. Chem. Soc., Washington, D.C., 1960.

⁸ S. F. Mason, *J. Chem. Soc.* **1954**, 2071.

⁹ R. F. Stewart and N. Davidson, *J. Chem. Phys.* **39**, 255 (1963).

¹⁰ P. de Santis, E. Giglio, and A. M. Liquori, *Nature* **188**, 46 (1960).

consistent approximations,¹¹ predicts that adenine, like its 9-methyl derivative, is major polarized along the shorter axis. The resultant effect of the dipoles spectroscopically is to give rise to a broad main band, the *x*-band, in the 230–280 $m\mu$ region of the ultraviolet absorption spectrum. As yet, the two individual components which make up this band cannot be attributed to the appropriate dipole until the direction of the major dipole in the molecule has been determined. With some simple purines a further narrow band, the *y*-band,⁸ around the 220 $m\mu$ region, is observed, but this was, until recently, outside the range of standard instruments and it as yet has provided no useful data on purine structures.

B. STRUCTURAL FEATURES DERIVED FROM SPECTROSCOPIC STUDIES

Spectroscopy, in both the ultraviolet and the infrared, and also the more recent nuclear magnetic resonance form, has been a useful tool in deciding structural configuration. The part played by infrared is self-evident, being used mainly to establish the presence or absence of functional groups. The infrared spectra of heterocycles including purines have been extensively reviewed.¹² Ultraviolet absorption spectroscopy, on the other hand, is less definitive in application but two features of purine structure have been studied by means of it. Variations in the spectrum with pH changes enable calculations of the basic and acidic dissociation constants to be made, from which the sites of proton capture or loss may be ascertained, whereas in cases where oxo-enol or amine-imine tautomerism is possible, the major component present may be determined by comparison with analogs in which the mobile hydrogen has been replaced by a methyl group.

Studies of tautomerism, in which the spectra of aminopurines and their substituted-amino analogs were compared, show clearly that the amino and not the imino form predominates.⁸ Confirmation has been supplied by infrared¹³ and by nuclear magnetic resonance studies on adenosine and guanosine.^{14,15} Alkylation of the pyrimidine ring nitro-

¹¹ H. Berthod and A. Pullman, *Compt. Rend.* **257**, 2738 (1963).

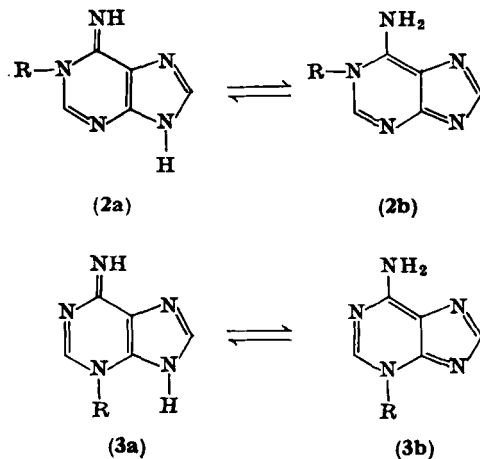
¹² A. R. Katritzky and A. P. Ambler, in "Physical Methods in Heterocyclic Chemistry" (A. R. Katritzky, ed.), Vol. II, Chapter 10. Academic Press, New York, 1963.

¹³ B. C. Pal and C. A. Horton, *J. Chem. Soc.* **1964**, 400.

¹⁴ J. P. Kokko, J. H. Goldstein, and L. Mandell, *J. Am. Chem. Soc.* **83**, 2909 (1961).

¹⁵ H. T. Miles, F. B. Howard, and J. Frazier, *Science* **142**, 1458 (1963).

gens in adenine gives the corresponding 1- and 3-*N*-alkyladenines, which on valence considerations can both be depicted in the 6-imino (2a, 3a) or 6-amino forms (2b, 3b). Physical evidence shows that whereas 1-methyladenine is present as the imino structure (2a, R = Me)¹⁶ the absence of an ionizable hydrogen in 3-methyladenine is presumed to indicate the presence of the amino isomer (3b, R = Me).¹³



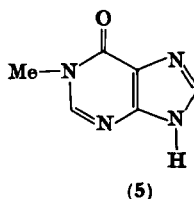
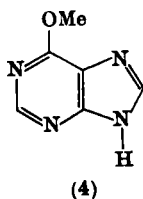
Generally speaking, the foregoing considerations cannot be applied to the spectra of the oxopurines as a means of deciding which tautomeric modification is present. The curves are usually simple in form,¹⁷ although cases exist where sufficient points of difference between the spectrum of an oxopurine and the corresponding methoxyl derivative lead one to presume that the oxo form^{8, 18} is the one present. Unfortunately, this evidence, by itself, is unreliable, as the spectrum of 6-methoxypurine (4), a molecule of the enol type, is very similar to that of 1-methylhypoxanthine (5), the isomeric oxo derivative.¹⁸ A likeness of this kind can be explained in terms of simplicity of molecular structure giving rise to single peak spectra falling, coincidentally, at the same wavelength.⁸ The main evidence that the oxo form predominates in oxopurines comes from infrared measurements made in the solid state¹⁹ and in deuterium oxide solution.¹⁵

¹⁶ P. Brookes and P. D. Lawley, *J. Chem. Soc.* **1960**, 539.

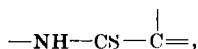
¹⁷ D. J. Brown and S. F. Mason, *J. Chem. Soc.* **1957**, 682.

¹⁸ G. B. Elion, *Ciba Found. Symp., Chem. Biol. Purines* p. 39 (1957).

¹⁹ S. F. Mason, *Ciba Found. Symp. Chem. Biol. Purines* p. 60 (1957).



The analogous purinethiones and their *S*-methyl derivatives, however, afford better spectral differences between their tautomeric forms than do the oxopurines. Evidence, taken from both ultraviolet¹⁹ and infrared,²⁰ supports the view that in 2-, and 6-, and 8-thiopurines the thione form predominates. A study²¹ in which the spectra of oxopurines are compared with the corresponding thione and in certain cases seleno derivatives shows that these heteroatoms are doubly bound to the ring carbon atom and that their influence on the spectrum is not uniform and varies with the position in the ring. Thus, replacement of the oxygen of a 6-oxopurine successively by sulfur and then selenium produces a bathochromic shift, whereas on repeating the process with a 2-oxopurine no such change is observed. It is proposed that these effects may be related to the fact that at the 6-position the adjacent atoms form part of an "amidic" system, i.e.,



whereas at the 2- and 8-positions the adjacent atoms are nitrogen, and a "uridic" structure, i.e., $-\text{NH}-\text{CS}-\text{N}(\text{H})-$, exists.

Spectral changes associated with pH variation, observed with 2-fluoropurine-6-thione, have been claimed²² to demonstrate the existence of a thiol-thione tautomerism. Thus, whereas alkaline solutions showed a thione-type spectrum, rather than the expected anionic form, on acidification a change, which took place at measurable rate, to the thiol form spectrum occurred. This effect has been attributed, by the authors, to the strong negative induction ($-I$) character of the 2-fluoro atom rendering the sulfur atom more electro-negative than the 1-nitrogen. Consequently, in acid solution the

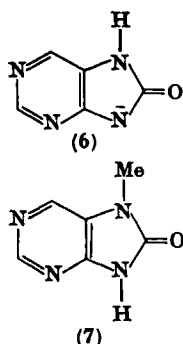
²⁰ C. H. Willets, J. C. Decius, K. L. Dille, and B. E. Christensen, *J. Am. Chem. Soc.* **77**, 2569 (1955).

²¹ H. G. Mautner and G. Bergson, *Acta Chem. Scand.* **17**, 1694 (1963).

²² J. A. Montgomery and K. Hewson, *J. Am. Chem. Soc.* **82**, 463 (1960).

former behaves abnormally and becomes the site of protonation. As proton capture is instantaneous, not time-dependent, a more logical explanation might lie either in protonation of a carbon atom or ring opening and recyclization occurring. Both of these are measurable rate reactions. The possibility of covalent hydration also exists, but the evidence for this occurring in purines is at present rather restricted.^{22a}

In simple purines the imidazole ring is usually involved in anion formation. The strong resemblance shown between the spectrum of the anion (6) of 8-oxopurine and that of 7-methyl-8-oxopurine (7)

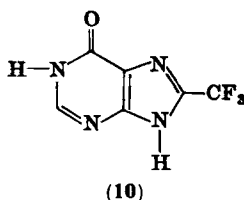
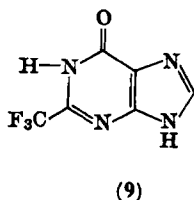
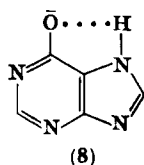


leads to the conclusion that dissociation at the 9-nitrogen has occurred.¹⁷ Evidence along these lines is obtained from comparisons of the alkaline spectra of 2- and 8-oxopurines with those of 2- and 8-aminopurines in neutral solution. The lack of correspondence between the spectra of the oxo and amino derivatives has been cited as an indication that ionization is probably associated with the five-membered ring.⁸ The converse appears to be true for hypoxanthine, the anionic spectrum of which is similar to that of the neutral molecule of adenine. Supporting evidence²³ suggests that dissociation gives rise to the same hydrogen-bonded anion (8), and the possibility that adenine may also form this type of internally bonded derivative would explain the spectral similarity. Attempts to resolve the site of proton loss in hypoxanthine have been made using the acid-strengthening properties produced by the insertion of fluorine atoms. Both the 2-trifluoromethyl- (9) and 8-trifluoromethylhypoxanthines (10) were

^{22a} A. Albert, Personal communication (1963).

²³ A. Albert, *Biochem. J.* **54**, 646 (1954).

examined in the hope that the derivative having the fluorine-containing group nearest to the ionization center would show the greatest lowering of the anionic dissociation constant. In practice, both derivatives showed a similar, and therefore inconclusive, decrease in value.²⁴ Studies on the spectra of methylated hypoxanthine derivatives have also failed to settle the point, the proton being lost with equal facility from the imidazole ring or the pyrimidine ring; ionization, therefore, is considered to be a function of the molecule as a whole rather than to be associated with a particular atom or group.²⁵



With di- and trioxapurines ionization is possible in either ring and can occur at more than one site in the molecule. Xanthine (2,6-dioxopurine) suffers first proton loss at the 3-position, this also being the case for its 1-methyl, 7-methyl, and 1,7-dimethyl derivatives.²⁶ With increasing pH values the dianion is formed by loss of a proton from the 7-position, and finally the 1-position is deprotonated. If the 3-position is already substituted, as in 3-methyl- and 1,3-dimethyl-xanthine, then the 7-nitrogen loses the first proton. Investigations of this type on uric acid (2,6,8-trioxopurine) and its derivatives show that the imidazole ring contains the most readily ionized hydrogen on the 9-nitrogen,²⁷ with second and third centers at the 3- and 1-positions, respectively.

One observation resulting from this work has been that ionization

²⁴ A. Giner-Sorolla and A. Bendich, *J. Am. Chem. Soc.* **80**, 5744 (1958).

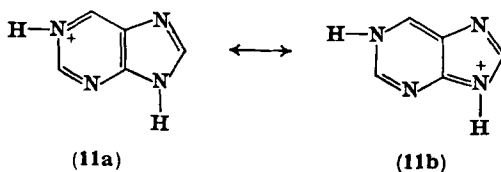
²⁵ G. B. Elion, *J. Org. Chem.* **27**, 2478 (1962).

²⁶ L. F. Cavalieri, J. J. Fox, A. Stone, and N. Chang, *J. Am. Chem. Soc.* **76**, 1119 (1954).

²⁷ F. Bergmann and S. Dikstein, *J. Am. Chem. Soc.* **77**, 691 (1955).

and methylation of xanthine and uric acid derivatives produce similar spectral effects,²⁷ an effect not unexpected, considering that removal of a proton or insertion of a methyl group will enhance the electron density of the associated nitrogen atom. The two types of spectra, although not necessarily alike in intensity, show wavelength changes of the same order. Thus the hypsochromic shift noted between a purine and its 1-methyl derivative is comparable with that seen when the purine undergoes proton loss at the 1-position. If ionization or alkylation occurs at any of the other nitrogen atoms, a bathochromic shift is observed. The fluorescence which is produced in solutions of guanosine and adenosine²⁸ at certain pH values is similar to that displayed by neutral solutions of corresponding methylated nucleosides²⁹ and correlations between sites of alkylation and ionization have been drawn.

Cation formation through proton addition can occur at various sites. Purine and its simple derivatives protonate in the pyrimidine ring.^{30, 31} Adenine, on the basis of results of studies on metal complex formation, is claimed to have the most basic nitrogen in the 6-amino group,³² but this conflicts with other work²³ showing that the pyrimidine ring is the preferred center for protonation as in other 6-substituted purines.³³ Simple adenine derivatives form the cation by proton addition at the 1-position, as do the 9-ribosyl analogs,¹⁶ but the 3-position is sometimes preferred, as in 2,6-diaminopurine.^{33a} A comparison of the ionization constants of 2- and 6-methylmercaptapurine shows N-1 to be the most basic nitrogen,³¹ the cation being stabilized through resonance forms, cf. **11a** and **11b**. Guanine, unlike



²⁸ H. C. Borresen, *Acta Chem. Scand.* **17**, 921 (1963).

²⁹ H. C. Borresen, *Acta Chem. Scand.* **17**, 2359 (1963).

³⁰ A. Bendich, P. Russell, and J. J. Fox, *J. Am. Chem. Soc.* **76**, 7063 (1954).

³¹ A. Albert, in "Physical Methods in Heterocyclic Chemistry" (A. R. Katritzky, ed.), Vol. I, Chapter 1. Academic Press, New York, 1963.

³² G. E. Cheney, H. Freiser, and Q. Fernando, *J. Am. Chem. Soc.* **81**, 2611 (1959).

³³ A. Giner-Sorolla and A. Bendich, *J. Am. Chem. Soc.* **80**, 3932 (1958).

^{33a} A. Veillard and B. Pullman, *J. Theoret. Biol.* **4**, 37 (1963).

adenine, protonates in the imidazole ring, with the 7-position being the most likely site. Evidence to support this comes from crystallographic studies (Section II, C).

C. STRUCTURAL FEATURES DERIVED FROM CRYSTALLOGRAPHIC STUDIES

Crystallographic examination of a number of purines, as the free bases, salts, or nucleotides, has been made using X-ray diffraction and two-dimensional Fourier techniques. The ring system is essentially planar, although exocyclic groups are sometimes encountered in out-of-plane positions. Apart from the architectural features obtained, two other points are noteworthy. Bond lengths can indicate the nature of the attached group, especially in those cases where tautomeric possibilities exist, even though the hydrogen atoms are not directly located. Secondly, the interbase distances in the crystal lattice are a guide to the probability of hydrogen-bonding occurring and can indicate the sites of protonation. These techniques are limited and give molecular details only for the solid state and cannot take environmental factors, such as solvent effects, into account.

Both adenine hydrochloride, as hemihydrate,³⁴ and guanine hydrochloride, as the hydrate,³⁵ show strong hydrogen-bonding in the lattice, linking together neighboring bases, water molecules, and hydrogen halides. Although each adenine unit is interbonded with all its adjacent units, the guanine cations³⁵ lie in sheets with only alternate layers connected, the same structure obtaining also with the dihydrated form of guanine hydrochloride.³⁶ Substitution at the 9-position of adenine and guanine salts inhibits direct hydrogen bond formation between the bases by preventing them from approaching near enough to form such linkages, this being due partly to the steric effect of the methyl group and partly to the mutual repulsion by the charge on each cation. This is seen with 9-methyladenine hydrobromide,³⁷ in which the hydrogen halides are linked through the 1- and 7-nitrogen atoms, but no interbase bonding occurs through the 3-position. The steric effect may not in itself be critical, since indirect evidence, obtained from polarized absorption spectra of thin crystals

³⁴ W. Cochran, *Acta Cryst.* **4**, 81 (1951).

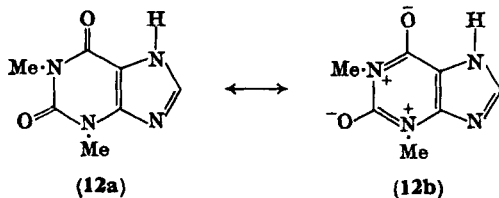
³⁵ J. M. Broomhead, *Acta Cryst.* **4**, 92 (1951).

³⁶ J. Iball and H. R. Wilson, *Nature* **198**, 1193 (1963).

³⁷ R. F. Bryan and K. I. Tomita, *Acta Cryst.* **15**, 1179 (1962).

of 9-methyladenine,⁹ suggests that the neutral molecule forms intermolecular hydrogen bonds at N-1 and N-7, giving rise to vertically stacked layers of bases. A similar case exists with 9-methylguanine dihydrobromide, which bonds, at the 7-position and the amino-group nitrogen, with the two hydrogen bromide molecules, but no interbase bonding occurs.³⁸ It has been shown also that both adenine and guanine in the solid state have amino rather than imino groups, whereas the carbon-oxygen linkage in guanine is predominantly double bond in character.³⁸ The adenine cation is shown to be protonated^{34, 37, 39} at N-1, whereas guanine and its 9-substituted derivatives³⁸ carry the proton at N-7. An unusual result was that adenosine-5'-phosphate was found to have a buckled ring system, this being ascribed to close packing distortion in the lattice between the base and the ribose-5'-phosphate group.³⁹

The methylated derivatives of xanthine and uric acid show the same planarity of the ring. With theophylline (1,3-dimethylxanthine) and caffeine (1,3,7-trimethylxanthine) the crystal architecture is so alike as to produce near crystal isomorphism.⁴⁰ Hydrogen bonding, of the normal type, is restricted because of nitrogen methylation, but evidence exists that methyl groups attached to nitrogen atoms possess hydrogens capable of involvement in bond formation⁴¹ of the type $=O \cdots H-CH_2-N=$. The bond lengths⁴² of 1,3-dimethylxanthine are similar to those in adenine, which indicates that fully methylated pyrimidine rings are mesomeric, and canonical forms of types **12a** and **12b** contribute.



In the theophylline neutral molecule the imidazole hydrogen is located at the 7-nitrogen atom, providing a bond with the 6-carbonyl group of a neighboring molecule, whereas the 9-nitrogen atom

³⁸ H. M. Sobell and K. I. Tomita, *Acta Cryst.* **17**, 126 (1964).

³⁹ J. Kraut, *Acta Cryst.* **16**, 79 (1963).

⁴⁰ D. J. Sutor, *Acta Cryst.* **11**, 453 (1958).

⁴¹ D. J. Sutor, *Acta Cryst.* **16**, 97 (1963).

⁴² D. J. Sutor, *Acta Cryst.* **11**, 83 (1958).

hydrogen bonds to a water molecule.⁴² If both imidazole nitrogens are methylated, as in 1,3,7,9-tetramethyluric acid, no such bonds occur and the molecule is anhydrous.⁴¹ Molecular packing in the crystal is changed from that of theophylline and caffeine, in that whereas these two bases are grouped in pairs in the same plane, tetramethyluric acid pairs off in the vertical plane¹⁰ with one of each pair reversed through 180°. This arrangement allows the mutual interaction of the strong transverse dipole, i.e., at right angles to the long axis of the molecule, to hold the pair together. Weaker hydrogen bonds may also arise from the *N*-methyl groups.

It has long been known⁴³ that the solubility of polycyclic hydrocarbons can be increased by the addition of purines to the solution. The degree to which this occurs increases proportionally with the area of the molecular envelope of the purine employed, the best results being obtained with methylated purines in which the area approximates to that of the hydrocarbon. Crystalline complexes between tetramethyluric acid and 3,4-benzopyrene and other polycyclics,⁴⁴ when subjected to X-ray diffraction methods, reveal 1:1 complexes in which purine and polycyclic hydrocarbon are stacked alternately in columns, an arrangement which emphasizes the planar nature of purines. Binding forces in the stack are most probably supplied by the dipolar nature of the purine and the induced polarity set up in the hydrocarbon by the purine. A similar situation seems to be present with riboflavine,⁴⁵ whose solubility is enhanced by the presence of caffeine or theophylline, both of which form 1:1 complexes with it. Significantly, the more methylated purine has the greater solubilizing effect, and this can be related to the decreasing possibility of the usual interpurine hydrogen bonding occurring as successive replacement of hydrogen atoms by methyl groups is made.

III. Nucleophilic and Electrophilic Substitution

The purine ring system undergoes substitution by both nucleophilic and electrophilic reagents, although with the latter the substituted atom is usually nitrogen rather than carbon. Attempts, made by various schools of theoretical chemistry, to predict the relative order

⁴³ E. Boyland and B. Green, *Biochem. J.* **83**, 12 (1963).

⁴⁴ P. de Santis, E. Giglio, A. M. Liquori, and A. Ripamonti, *Nature* **191**, 900 (1961).

⁴⁵ D. E. Guttman and M. Y. Athalye, *J. Am. Pharm. Assoc.* **49**, 687 (1960).

of attack by such reagents have been only partially successful, as it is not possible to take all factors into account, the calculations generally applying to the isolated molecule⁴⁶ divorced from environmental influences such as polarizing groups and ionization or solvent effects.⁴⁷ Various criteria have been used to express the electron state of the atoms, including Hückel charge densities,^{48, 49} frontier electron densities,⁵⁰ free valence indices,⁴⁸ and localization energies.^{51, 52} The majority of the calculations were of the linear combination of atomic orbital-molecular orbital (L.C.A.O.-M.O.) type, but refinements by one school using the semi-empirical self-consistent molecular orbital (S.C.M.O.) method have given orders of activity which agreed with some experimental results.⁵³

1. Nucleophilic Substitution

Fischer,^{54, 55} many years ago, showed that strong bases react with the halogen atoms of 2,6,8-trichloropurine sequentially, the order of replacement being first at the 6-, then at the 2-, and lastly at the 8-position. Attempts to justify this order using theoretical treatment have been made. However, no data for trichloropurine are available, but localization energy calculations,⁵⁶ made on purine itself, agree with the above order of substitution. Various nuclear magnetic resonance (NMR) studies made on purines and their deuterated analogs,^{52, 57, 58} in polar and nonpolar solvents, have not been unanimous as to the location of the most active carbon atom. The majority^{57, 58} view, however, favors the order of activity observed practically, i.e., C-6, C-2, and C-8.

⁴⁶ P. G. Lykos and R. L. Miller, *Tetrahedron Letters* No. 25, 1743 (1963).

⁴⁷ B. Pullman, *J. Org. Chem.* **29**, 508 (1964).

⁴⁸ S. F. Mason, *Ciba Found. Symp. Chem. Biol. Purines*, p. 72 (1957).

⁴⁹ A. Pullman and B. Pullman, *Bull. Soc. Chim. France* **1958**, 766.

⁵⁰ K. Fukui, T. Yanezawa, and H. Shingu, *J. Chem. Phys.* **20**, 722 (1952).

⁵¹ K. Fukui, T. Yanezawa, C. Nagata, and H. Shingu, *J. Chem. Phys.* **22**, 1433 (1954).

⁵² A. Veillard, *J. Chim. Phys.* **59**, 1056 (1962).

⁵³ R. L. Miller, P. G. Lykos, and H. N. Schmeising, *J. Am. Chem. Soc.* **84**, 4623 (1962).

⁵⁴ E. Fischer, *Ber. Deut. Chem. Ges.* **30**, 2220 (1897).

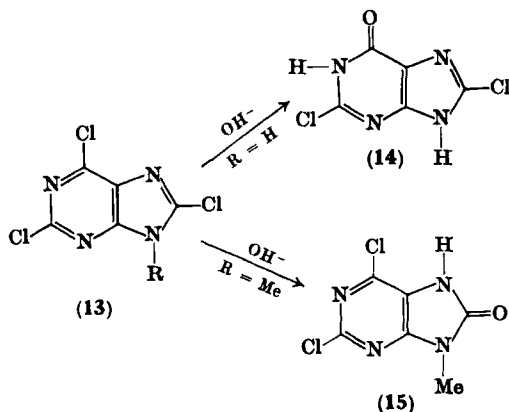
⁵⁵ E. Fischer, *Ber. Deut. Chem. Ges.* **30**, 2226 (1897).

⁵⁶ B. Pullman, *J. Chem. Soc.* **1959**, 1621.

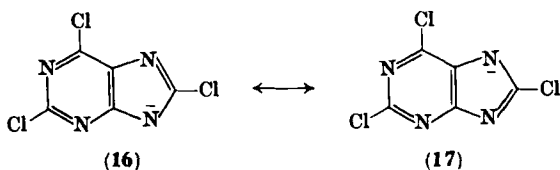
⁵⁷ S. Matsuura and T. Goto, *Tetrahedron Letters* No. 22, 1499 (1963).

⁵⁸ M. P. Schweizer, S. I. Chan, G. K. Helmkamp, and P. C. P. Ts'o, *J. Am. Chem. Soc.* **86**, 696 (1964).

If the 7- or 9-methyl derivative of 2,6,8-trichloropurine (13) is treated with a strong base, substitution occurs at the 8- (15) and not the 6-position (14) as above.⁵⁹ This result is the opposite of what might be expected as the inductive effect of the methyl group should increase the electronegativity of the imidazole ring and direct nucleophilic attack into the pyrimidine ring. This apparently anomalous behavior



has been the subject of detailed investigation^{60,61} and nucleophilic attack has been studied on trichloropurines both with and without alkyl groups on the imidazole nitrogens. The results obtained have led to the general theory that the ionic state of the molecule at the moment of substitution decides the orientation of the attack. In unsubstituted trichloropurine, ionization of the imidazole hydrogen,



due to the base present, gives rise to the stabilized resonance forms 16 and 17. As anion formation increases the electron-density in the imidazole moiety the 8-position is deactivated and the nucleophile is directed to the 6-position instead. When the same reaction is carried

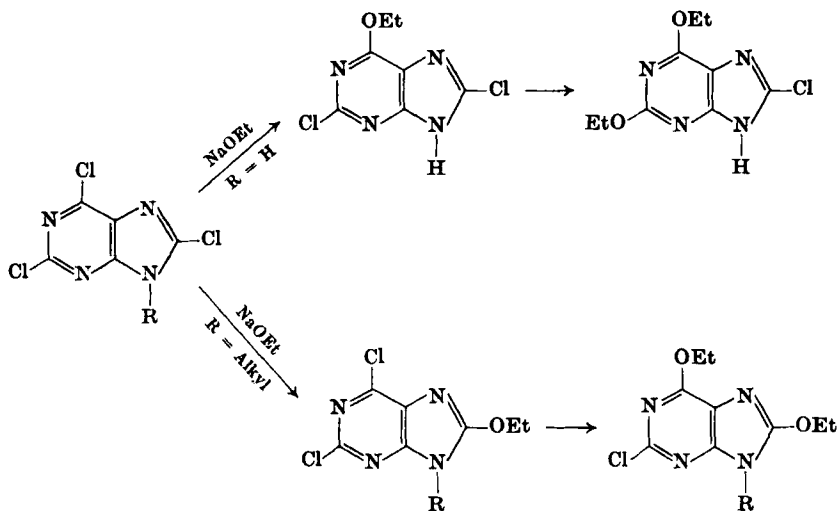
⁵⁹ E. Fischer, *Ber. Deut. Chem. Ges.* **30**, 1846 (1897).

⁶⁰ A. G. Beaman and R. K. Robins, *J. Org. Chem.* **28**, 2310 (1963).

⁶¹ E. J. Sutcliffe and R. K. Robins, *J. Org. Chem.* **28**, 1662 (1963).

out with a 7- or 9-alkylated trichloropurine, proton loss is not possible and the 8-carbon reacts first. If a strong nucleophile possessing no pronounced basic character is used, then again anion formation does not occur and both 6- and 8-positions may be substituted. This is shown by the reaction of thiourea and 2,6,8-trichloropurine which gives 2-chloropurine-6,8-dithione.⁶²

The ion formation theory also provides an explanation for the fact that strong alkali fails to hydrolyze 8-chloropurine,⁶³ whereas even weak alkali rapidly converts the 6-chloro analog to hypoxanthine. Similarly, as expected, both 2,6- and 6,8-dichloropurine are hydrolyzed only at the 6-position. By using an easily removable blocking group such as tetrahydropyranyl at the 9-position of trichloropurine, it is possible to prepare either 6- or 8-substituted derivatives as required.⁶¹ (Scheme 1)



SCHEME 1

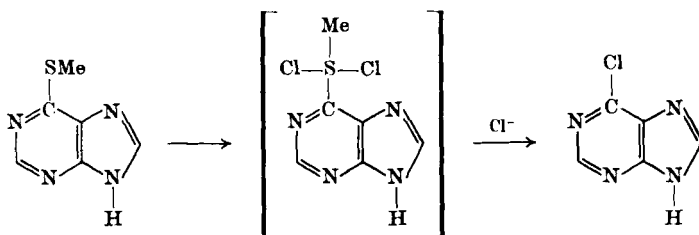
Anomalous behavior is shown by 2,8-dichloropurine which, having no chlorine at the 6-position, might be expected to undergo substitution at the 2-carbon. This is not so, as methylamine and methanethiol give rise to the corresponding 2-chloro-8-methylamino- and 2-chloro-8-methylthiopurine.⁶⁴ The lack of reactivity shown by the chlorine

⁶² H. Ballweg, *Ann.* **649**, 114 (1961).

⁶³ A. G. Beaman and R. K. Robins, *J. Appl. Chem.* **12**, 432 (1962).

⁶⁴ A. F. Lewis, A. G. Beaman, and R. K. Robins, *Can. J. Chem.* **41**, 1807 (1963).

analogs using chlorine has been shown to be acid-dependent. All three thione groups were replaced when chlorine was bubbled through a methanolic solution of 2,6,8-trimethylthiopurine containing hydrogen chloride.⁶⁷ The mechanism evolved for this reaction (Scheme 2) postulates that the group undergoing nucleophilic replacement by the chloride ion is derived from chlorination of the methylthio group. In such a group the electron-withdrawing properties of the sulfur enhance the positive nature of the carbon to which it is attached, so facilitating substitution by the chloride ion.⁶⁸ The order of replacement of thione by chlorine follows the general sequence for nucleophilic attack under acid conditions, that is, first the 8-, then the 6- and



SCHEME 2

the 2-positions. So far only fairly clear-cut examples of the behavior of ionic species toward nucleophilic attack have been considered. These, however, probably oversimplify the case as other considerations must also be taken into account, the most important of which are the directive effects of substituent groups in the reactant purine. Such group effects must be considered according to the cyclic atom, whether carbon or nitrogen, to which they are attached.

2. Nucleophilic Reactions of C-Substituted Purines

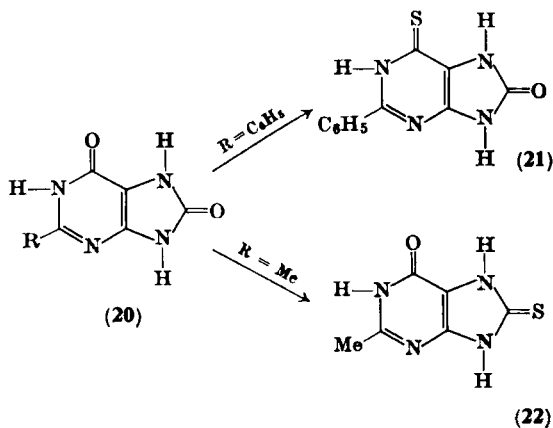
The influence exerted on the π -electron structure by insertion of a group with either pronounced electron-withdrawing or -releasing character may be apparent in either the five- or the six-membered ring, irrespective of the position of the substituent in the molecule, although it follows that the effect is usually more noticeable the nearer the reacting site is to the substituent. By insertion of suitable electron-releasing groups into fluorinated derivatives, the electrophilic nature of the fluorine atoms can be offset; for example, the

⁶⁷ R. K. Robins, *J. Org. Chem.* **26**, 447 (1961).

⁶⁸ C. W. Noell and R. K. Robins, *J. Am. Chem. Soc.* **81**, 5997 (1959).

dissociation constants of 2-amino-6,8-bis-trifluoromethylpurine are similar to those of 8-trifluoromethylpurine.²⁴ The amino group nullifies the effect of the trifluoromethyl group at the 6-position. The strong electronegativity of fluorine renders any carbon to which it is attached highly susceptible to nucleophiles. Thus, 2-fluoroadenosine with butylamine readily forms the 2-butylamino derivative²² and contrasts with the 2-chloro analog which is virtually inert.

Purines bearing alkyl or aryl substituents normally show the reactions of the corresponding unsubstituted analogs, but some differences have been noted between 2-methyl- and 2-phenylpurines under the same reaction conditions.^{69, 70} Although the phenyl group can function as an electron source or sink, neither of these effects is



apparent in the reaction behavior of 2-phenylpurines, which is the same as for the unsubstituted purines.⁷⁰ On the other hand, the 2-methyl analogs show anomalous behavior.⁷¹ Whereas 6,8-dioxo-purines of the type **20** normally thiate at the 6-position only^{65, 72} (**21**), the 2-methyl derivative (**20**, R = Me) gives the purine-8-thione (**22**), capable of further thiation to purine-6,8-dithione.⁷¹ The inert nature of a 6-oxo group in 2-methylpurines is also seen in the resistance to thiation of 2-methylhypoxanthine, when under similar conditions

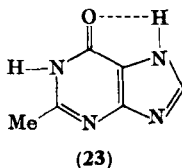
⁶⁹ C. W. Noell and R. K. Robins, *J. Org. Chem.* **24**, 320 (1959).

⁷⁰ F. Bergmann, A. Kalmus, H. Ungar-Waron, and H. Kwietny-Govrin, *J. Chem. Soc.* **1963**, 3729.

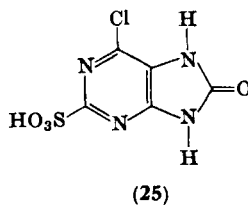
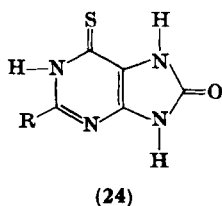
⁷¹ F. Bergmann and A. Kalmus, *J. Chem. Soc.* **1962**, 860.

⁷² F. Bergmann and A. Kalmus, *J. Org. Chem.* **26**, 1660 (1961).

hypoxanthine is readily converted to purine-6-thione.⁷¹ The lack of reactivity at the 6-position is attributed to a stronger hydrogen-bond bridge (**23**), formed between the oxygen atom on the 6-carbon and the protonated 7-nitrogen,⁷¹ which is strengthened by the inductive effect of the methyl group.



The presence of oxo groups in the ring tends to deactivate the remaining positions, the effect being strongest in 8-oxopurines where failure to hydrolyze the chlorine of 2-chloro-8-oxopurine-6-thione⁶⁷ (**24**, R = Cl) is due to the increased electron-density at the 2-carbon produced by the oxo group. However, replacement of the chlorine by a sulfonic acid group (**24**, R = SO₂OH) activates the 2-position by a -I effect and nucleophilic displacement by OH⁻ becomes possible.⁷³ Although the electron-attracting property of the sulfonic acid group can reduce the electron-density of the attached carbon, the effect does not appear to be transmitted around the ring, as the 6-position in 6-chloro-8-oxopurine-2-sulfonic acid (**25**) is resistant to hydrolysis.⁶⁷



A similar ring deactivation is produced by a 6-oxo group as in 6-oxo-purine-2,8-dithione, the thione groups of which cannot be replaced by chlorine under neutral conditions. If the pH of the reaction mixture is lowered, the ensuing protonation of the ring activates the two positions sufficiently to permit displacement of the thione groups by chloride ion.⁶⁷ Only at the 6-position do the dioxopurines^{65, 72, 74} and

⁷³ G. B. Elion, S. Mueller, and G. H. Hitchings, *J. Am. Chem. Soc.* **81**, 3042 (1959).

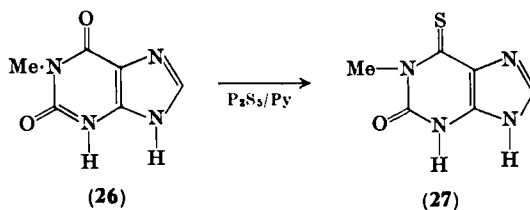
⁷⁴ A. G. Beaman, *J. Am. Chem. Soc.* **76**, 5633 (1954).

uric acid⁷³ show activity toward thiation, the resulting 6-thione derivatives not undergoing further substitution of oxygen by sulfur. With 2,8-dioxopurine, which has no replaceable oxo group at the 6-position, no reaction occurs,⁷² as was also found with 8-oxo-2-methylpurine⁷¹; in both cases the group in the 2-position has electron-releasing character. Direct thiation of a 6-oxopurine is very facile if the reacting purine already has a thione group in the 2-⁷⁴ or 8-position⁷¹ or both.⁶⁸

3. Nucleophilic Reactions of *N*-Substituted Purines

A more pronounced effect on the π -electron structure is produced by *N*-alkylation than by C-substitution, replacing the ring nitrogen proton by alkyl groups restricts the number of anionic forms and of tautomeric structures. The alkylated purines can be stabilized toward base attack by anion formation, but if no proton is available then fission of one of the rings is likely.

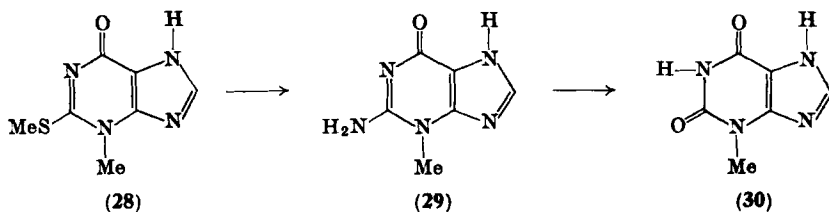
Purines alkylated at N-1 are not common, those of adenine readily undergoing intramolecular rearrangement²⁵ with alkali affording good examples of the Dimroth rearrangement (see Section III, 4). In their general reactions they resemble their unmethylated derivatives, for example, 1-methylxanthine (26), like xanthine,⁷⁴ thiates only at the 6-position²⁵ (27).



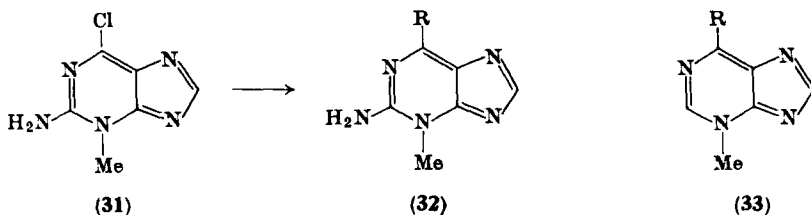
The isomeric 3-alkylpurines, in contrast to the parent compounds, are highly reactive at the 2- and 6-carbon atoms. The susceptibility of the 2-carbon to nucleophilic attack is shown by the facility with which 6-oxo-3-methyl-2-methylmercaptapurine (28) is converted by ammonia into the 2-amino (29) and then with alkali into the 2-oxo (30) derivative.⁷⁵ This reaction sequence explains why the action of aqueous ammonia on the 2-methylmercaptapurine (28) resulted in the isolation of 3-methylxanthine (30) rather than the required

⁷⁵ L. B. Townsend and R. K. Robins, *J. Am. Chem. Soc.* **84**, 3008 (1962).

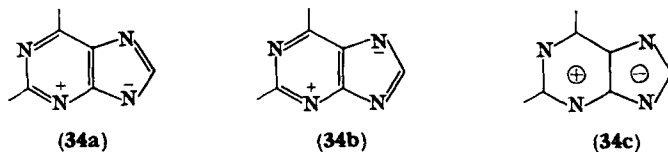
3-methylguanine (29).²⁵ With similar facility, the group or atom at the 6-position can be replaced as in the case of 2-amino-6-chloro-3-methylpurine (31), which gives the 6-ethoxy (32, R = OEt), 6-butylthio (32, R = SBut), and 6-amino (32, R = NH₂) analogs⁷⁵ with the appropriate reagent, whereas 2-amino-6-chloropurine is inert toward



them. Other workers have demonstrated the conversion, under milder conditions, of 3-methyl-6-methylthiopurine (33, R = SMe) to the corresponding 6-oxo (33, R = OH) and 6-amino (33, R = NH₂) derivatives.⁷⁶ The unusual electrophilic character displayed by the 2- and 6-carbon atoms cannot be explained using the classic "fixed



bond" structure of the type 33, which suggests that the enhancement of the electron-density in the pyrimidine moiety, owing to the +I effect of the methyl groups, should deactivate the carbon atoms. The susceptibility to nucleophilic attack is best accounted for by resonance structures 34a and 34b in which depletion of the π -electrons of the pyrimidine ring is occasioned by the electron-withdrawing effect of



⁷⁶ J. W. Jones and R. K. Robins, *J. Am. Chem. Soc.* **84**, 1914 (1962).

the quaternary nitrogen. The simplified structure **34c** represents an over-all electron-deficient pyrimidine ring, containing two electrophilic centers.⁷⁵ The resistance of the 2- and 6-amino groups in 3-methylpurines^{75, 76} to conversion to oxo by nitrous acid may be due to the formation of deactivated protonated species.

The order of substitution of trichloropurines alkylated in the pyrimidine ring differs from that in non-alkylated purines in that the first halogen replaced by a basic group is at the 8-position, followed by the 6- and then the 2-position. The result of alkylation in the imidazole ring, i.e., at the 7- or 9-position, is that anionic dissociation cannot now occur, and attack by hydroxyl ions is again at the 8-position.^{59, 60} If no substitution is possible at this site, then the 6-position is involved. Both 7-methyl,⁷⁷ and 9-methyl⁷⁸ and 9-phenyl⁷⁹ derivatives of 2,6-dichloropurine give the appropriate 2-chloro-6-oxopurine. Replacement of chlorine by fluorine, using silver fluoride, was not successful with some chloropurines, but their 7- or 9-methyl homologs readily gave the fluorinated analogs.⁶⁰ It is possible that formation of a silver salt, in the case of the non-methylated purines, results in a general ring deactivation.

It has been mentioned²⁷ (Section II, B) that removal of a proton from a ring nitrogen in purinones causes a similar spectral shift in the ultraviolet to that observed when the same nitrogen is methylated. Although this effect in both cases is due to the increased electron-density set up in the nitrogen atom, the disturbances induced in the electron configuration of the purine as a whole do not seem to be comparable. Thus, for example, after methylation of an imidazole nitrogen the site of first nucleophilic substitution (8-position) is different from that when the anion is used (6-position).^{61, 62}

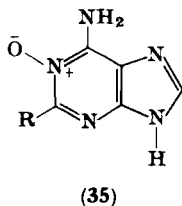
Activation of some sites, which are normally inert, can occur through oxide formation taking place at an adjacent nitrogen atom. The induced positive charge on the oxygen-bearing nitrogen effectively reduces the electron-density of the neighboring carbon atom, for whereas the chlorine atom in 2-chloroadenine is inert toward hydrolysis, that of the *N*-oxide (**35**, R = Cl) is readily converted to the oxide of isoguanine (**35**, R = OH).⁸⁰ The 2-methylsulfinyl derivative (**35**, R = MeSO) reacts likewise.⁸⁰

⁷⁷ E. Fischer, *Ber. Deut. Chem. Ges.* **31**, 431 (1898).

⁷⁸ J. M. Gulland and L. F. Storey, *J. Chem. Soc.* **1938**, 692.

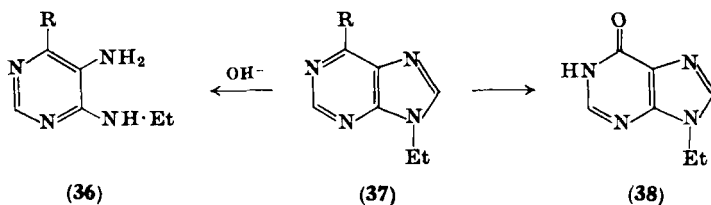
⁷⁹ H. C. Koppel and R. K. Robins, *J. Am. Chem. Soc.* **80**, 2751 (1958).

⁸⁰ R. M. Cresswell and G. B. Brown, *J. Org. Chem.* **28**, 2560 (1963).



4. Nucleophilic Substitution Leading to Degradation or Rearrangement

a. *Degradation.* Many examples exist of mild alkaline or acid treatment causing degradation^{13,81,82,83} to pyrimidine, or more usually, imidazole derivatives. More vigorous conditions result in complete breakdown to ammonia and glycine.⁸⁴ Stability toward alkali is a feature of oxo derivatives and purines containing electron-releasing groups, while N-alkylation, which may prohibit anion formation, has the opposite effect. This is seen in the high stability of xanthine to long heating in alkali and the rapid breakdown of caffeine under similar conditions.⁸⁵ Parallel behavior is shown by purine, which is resistant to alkaline attack, and the 9-methyl analog which is quickly



destroyed by this treatment.⁸⁵ Alkaline hydrolysis of 6-chloro-9-ethylpurine⁸⁶ (37, R=Cl), having no strong electron-donating groups and having no anionic form, would be expected to form a 4,5-diaminopyrimidine of type 36 as do other 9-alkylpurines,^{85,86} for example 37 (R=H), through nucleophilic attack at the 8-carbon. However, hydrolysis of the chlorine precedes this reaction and the resulting hypoxanthine (38) formation stabilizes the molecule against

⁸¹ E. Fischer, *Ber. Deut. Chem. Ges.* **31**, 3266 (1899).

⁸² H. Biltz and H. Rakett, *Ber. Deut. Chem. Ges.* **61**, 1409 (1928).

⁸³ E. N. Shaw, *J. Am. Chem. Soc.* **80**, 3899 (1958).

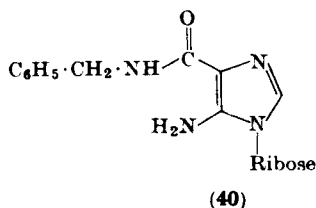
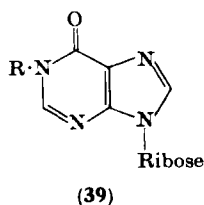
⁸⁴ R. H. Lindsay, W. H. Paik, and P. P. Cohen, *Biochim. Biophys. Acta* **58**, 585 (1962).

⁸⁵ A. Albert and D. J. Brown, *J. Chem. Soc.* **1954**, 2060.

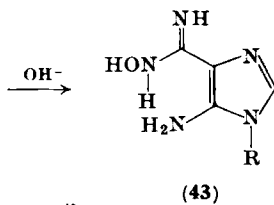
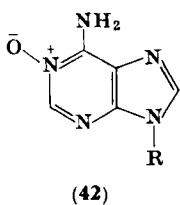
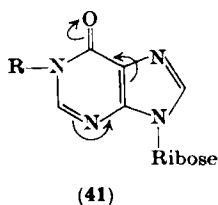
⁸⁶ J. A. Montgomery and C. Temple, *J. Am. Chem. Soc.* **79**, 5238 (1957).

further attack. The presence of even traces of methanol in this reaction, if carried out at room temperature, leads to preferential formation of 6-methoxypurine.⁸⁷

The instability of simple purine ribosides toward alkali^{88,89} can be related to the fairly strong electron-withdrawing power of the ribose moiety, which directs the nucleophile to the 8-carbon. Stabilization of a nucleoside can be achieved if anion formation is possible. This is seen with inosine (hypoxanthine-9-D-ribose) (**39**, R = H), which is



stable but becomes labile when converted to the 1-*N*-benzyl derivative⁷⁰ (**39**, R = CH₂C₆H₅), the pyrimidine ring being cleaved (**40**). The corresponding 6-thioinosine is likewise degraded,⁹⁰ as are other *N*-alkylated purines, to the imidazole.^{13,81,82,83,91,92} The change of electrophilic center from the 8- to the 2-carbon may be a consequence of two mutually reinforcing effects, one being a general ring activation produced by the ribose moiety, the other a direct influence on the 2-carbon of the type **41**. Similar electron disturbances operate in adenosine-1-oxide (**42**), the 2-carbon of which is rendered more



R = D-ribose

⁸⁷ J. A. Montgomery and C. Temple, *J. Am. Chem. Soc.* **83**, 630 (1961).

⁸⁸ B. R. Baker and K. Hewson, *J. Org. Chem.* **22**, 959 (1957).

⁸⁹ M. P. Gordon, V. S. Weliky and G. B. Brown, *J. Am. Chem. Soc.* **79**, 3245 (1957).

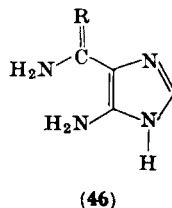
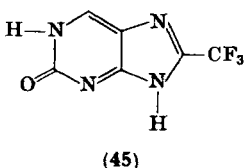
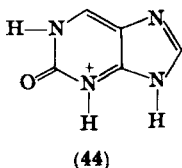
⁹⁰ J. A. Montgomery and H. J. Thomas, *J. Org. Chem.* **28**, 2304 (1963).

⁹¹ S. Golovchinskaya, O. A. Kolganova, L. A. Nikolaeva, and E. S. Chaman, *Zh. Obshch. Khim.* **33**, 1650 (1963).

⁹² A. M. Bellini, *Ann. Chim. (Rome)* **51**, 1409 (1961).

electron-demanding by the positive charge on the neighboring nitrogen. Cleavage to the imidazole (43) occurs with alkali, but removal of the ribosyl group first gives the alkali-stable adenosine-1-oxide,⁹³ the molecule being stabilized by anion formation.

Purines have been extensively studied under acid conditions⁸⁵; stability increases with the number of electron-releasing substituents present. Monosubstituted purines, especially those with a group at the 2-position, tend to be acid-labile, giving the appropriate 4,5-diaminopyrimidine. That degradation occurs primarily in the imidazole ring suggests that the pyrimidine ring is stabilized by protonation involving cationic forms such as 44. If the electrophilicity of the 8-carbon is strengthened by substitution of a trifluoromethyl group, the resulting 2-oxo-8-trifluoromethylpurine (45)⁹⁴ is



rapidly broken down at pH 2. The fact that adenine and guanine, on the other hand, are degraded by boiling acid to the imidazoles 46 (R = NH or O) may explain why the amino group in adenine is readily replaced by substituted amines⁹⁵ if amine salts, rather than the free bases, are used. The mechanism proposed for this exchange reaction involves fission and recyclization of the pyrimidine ring and could operate by way of the formyl derivative of 46 (R = NH).

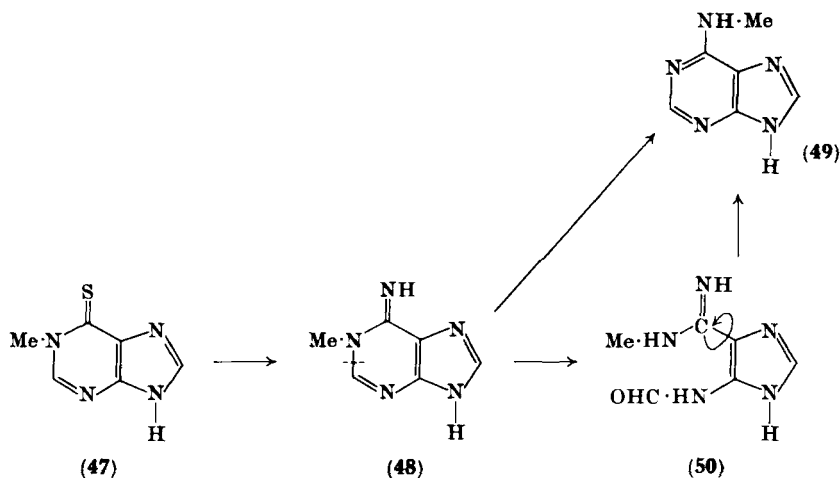
b. *Rearrangement.* The most widely encountered purine rearrangement occurs with adenine derivatives involving the apparent migration of an alkyl group from the 1-nitrogen to the exocyclic nitrogen. This reaction, which occurs in other heterocyclic systems (the Dimroth rearrangement), was first noted¹⁸ in a purine when amination of 1-methylpurine-6-thione (47) was attempted, the product being 6-methylaminopurine (49) rather than the expected 6-imino-1-methylpurine (48). A mechanism for this rearrangement followed

⁹³ M. A. Stevens, H. W. Smith, and G. B. Brown, *J. Am. Chem. Soc.* **81**, 1734 (1959).

⁹⁴ A. Albert, Personal communication (1963).

⁹⁵ C. W. Whitehead and J. W. Traverso, *J. Am. Chem. Soc.* **82**, 3971 (1960).

from the observation that treatment of 1-methyladenine with hot ammonium hydroxide gave 6-methylaminopurine,¹⁶ indicating that conversion of thione to methylaminopurine must have taken place through the intermediate iminopurine (48). Other 1-*N*-alkyl adenines also undergo this rearrangement,^{90,96,97} which is envisaged²⁵ as an initial attack by a hydroxyl ion on the 2-carbon causing fission of the pyrimidine ring at bond N-1—C-2 (48) followed by rotation of the amidine group around the C-5—C-6 bond (50) and recyclization. The same type of mechanism has been proposed for a methyl migration from an endocyclic to exocyclic nitrogen in a pyrimidine.⁹⁸ If alcoholic



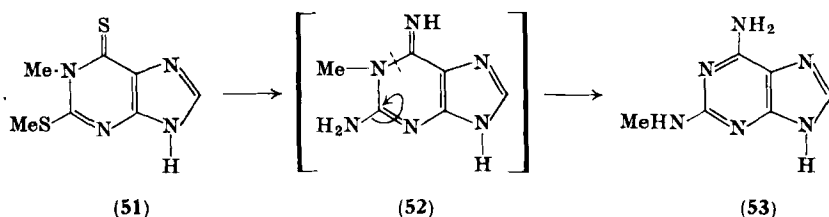
instead of aqueous ammonia is used on 1-methylpurine-6-thione (47) and prolonged heating adopted, the main product is adenine. Two pathways, which differ only in the stage at which the secondary amino group is replaced by the primary, are suggested.²⁵ No strong evidence in favor of either pathway is available, but it is noteworthy that with alcoholic ammonia under milder conditions 6-methylaminopurine is formed.²⁵ Although the same alkali-induced rearrangement is noted with 1-methylpurine-2,6-dithione giving 6-methylaminopurine-2-thione, the analog having the 2-methylthio group undergoes a different rearrangement, with group changes at both 2- and 6-positions. Thus, 1-methyl-2-methylthiopurine-6-thione (51) with hot

⁹⁶ E. C. Taylor and P. K. Loeffler, *J. Org. Chem.* **26**, 1861 (1961).

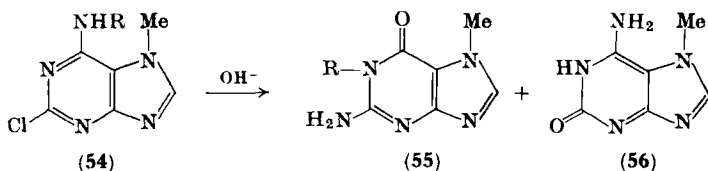
⁹⁷ H. G. Windmueller and N. O. Kaplan, *J. Biol. Chem.* **236**, 2716 (1961).

⁹⁸ D. J. Brown, *Nature* **189**, 828 (1961).

aqueous ammonia is converted to 6-amino-2-methylaminopurine (**53**), the mechanism appearing to require first the formation of the expected 2-amino-6-imino-1-methylpurine (**52**). The latter then suffers attack by ammonia at the 6-carbon, and the ensuing ring fission is followed by rotation of the methylguanidino group about the C-2—N-3 bond and recyclization.²⁵



A further example (the oldest recorded) of isomerization, which differs from the preceding two examples, is credited to Fischer,⁹⁹ who attempted the hydrolysis of the chlorine atom of 6-amino-2-chloro-7-methylpurine (**54**, R = H) with alkali but obtained 7-methylguanine (**55**, R = H) instead of 7-methylisoguanine. Some insight into the intramolecular rearrangement may be gained from the fact that the

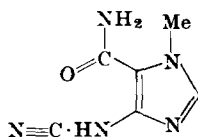


6-methylaminopurine (**54**, R = Me) under this treatment gives 1,7-dimethylguanine (**55**, R = Me). This suggests that one stage of the process involves nucleophilic attack at the 6-carbon and rotation about the C-5—C-6 bond of the carboxamide group formed. The reaction mechanism has been studied without conclusive results being obtained,¹⁰⁰ but the intermediate **57** is proposed. One surprising discovery arising from this investigation is that some 7-methylisoguanine (**56**) is formed in small amounts but it is not derived by a simple substitution of chlorine by a hydroxyl group but by way of the imidazole derivative (**58**).¹⁰⁰ A rearrangement of this type occurs with

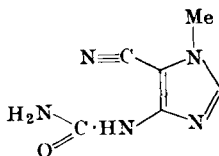
⁹⁹ E. Fischer, *Ber. Deut. Chem. Ges.* **31**, 542 (1898).

¹⁰⁰ E. Shaw, *J. Org. Chem.* **27**, 883 (1962).

the isomeric 4-amino-6-chloro-1-methylpyrazolo(3,4-*d*)pyrimidines and the mechanism postulated could apply to both classes of compound.¹⁰¹



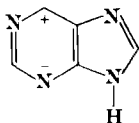
(57)



(58)

5. Enzymic Oxidation of Purines

The major studies in this field are the work of one group¹⁰² using mainly *in vitro* techniques. The action of xanthine oxidase (XO), a milk enzyme, converts purine through hypoxanthine and xanthine to uric acid, in which the order of oxidation is seen to be the same as for base substitution of 2,6,8-trichloropurine. It was first held that the nucleophilic reagent responsible was water, which added across the double bonds and resulted in dihydropurines which then lost hydrogen, so restoring the aromaticity of the system.¹⁰³ This view has now been modified and hydroxyl-ions are assumed to be the nucleophiles.¹⁰⁴ As purine contains no substituents, directive influences are supplied by the dipolar forms extant at the time of reaction, of which **59** represents



(59)

the hybrid form with an aromatic imidazole ring and an electrophilic 6-carbon.¹⁰⁴ The susceptibility of this carbon to nucleophilic substitution is indicated by nuclear localization energy (NLE) calculations,¹⁰⁵

¹⁰¹ C. C. Cheng and R. K. Robins, *J. Org. Chem.* **24**, 1570 (1959).

¹⁰² F. Bergmann, H. Kwietny, G. Levin, and D. J. Brown, *J. Am. Chem. Soc.* **82**, 598 (1960).

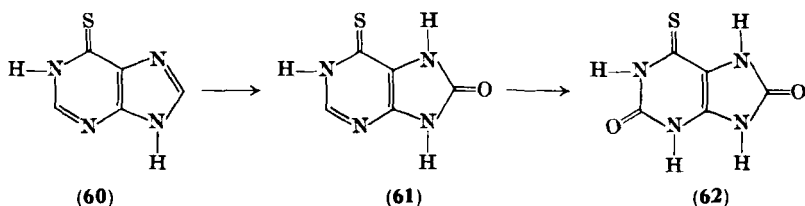
¹⁰³ F. Bergmann and S. Dikstein, *J. Biol. Chem.* **223**, 765 (1956).

¹⁰⁴ F. Bergmann, H. Ungar, and A. Kalmus, *Biochim. Biophys. Acta* **45**, 49 (1960).

¹⁰⁵ A. M. Perrault, C. Valdemoro and B. Pullman, *J. Theoret. Biol.* **1**, 180 (1961).

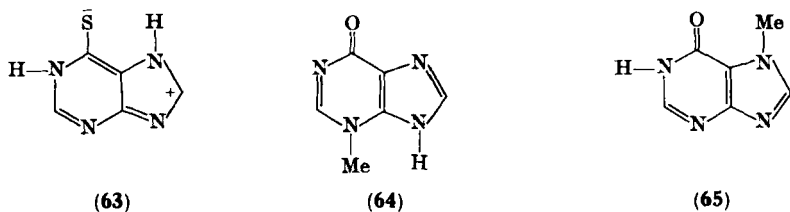
which in this case may bear some relationship to the true electronic state of the molecule as the enzyme reactions take place under near neutral conditions. Nevertheless, the possibility of modification of the electron distribution in the purine, due to the interaction with the receptor surface, must also be borne in mind.

Enzymic oxidation pathways vary with the substrate molecule, for purine-6-thione (**60**), although being fully oxidized to 6-thiouric acid (**62**), undergoes displacement first at the 8-carbon (**61**) rather than at



the 2-carbon as with hypoxanthine. The activity of the 8-position in purine-6-thione is associated with the weak electronegative character of the sulfur atom giving rise to resonance forms of type **63**.¹⁰⁶

Purine-6-thione, in forming the 8-oxopurine, behaves like other 6-substituted purines¹⁰⁶⁻¹⁰⁸ used with this enzyme system. The exception to the rule is hypoxanthine which suffers attack at the



2-position. Calculation of NLE values shows this to be the most favorable site¹⁰⁵ if the neutral molecule reacts in the oxo form. Furthermore, stabilization and activation of the 2-position may be a

¹⁰⁶ F. Bergmann and H. Ungar, *J. Am. Chem. Soc.* **82**, 3957 (1960).

¹⁰⁷ J. B. Wyndgaarden and J. T. Dunn, *Arch. Biochem. Biophys.* **70**, 150 (1957).

¹⁰⁸ F. Bergmann, H. Ungar-Waron, H. Goldberg, and A. Kalmus, *Arch. Biochem. Biophys.* **94**, 94 (1961).

consequence of intramolecular hydrogen-bonding between oxygen and the 7-nitrogen¹⁰² in which the proton donor is the imidazole hydrogen. Support for this idea comes from the fact that enzymic treatment of 3-methylhypoxanthine, which has the fixed oxo structure **64**, gives 3-methylxanthine, whereas 7-methylhypoxanthine¹⁰⁰ (**65**) and 3-methylpurine-6-thione,¹⁰⁹ which has a reduced chance of forming a hydrogen-bonded complex due to the weak electronegative nature of the sulfur atom, both remain unchanged. Evidence has been presented to show that the most active tautomeric form of the substrate molecule is decided by the mode of attachment to the enzyme receptor surface. If the enzyme clostridial xanthine dehydrogenase is used with hypoxanthine, 6,8-dioxopurine results. This activation of the 8-carbon instead of the more usual 2-carbon has been suggested as being due to the adoption by hypoxanthine of the hydrogen-bonded enol configuration when positioned at the receptor surface of the enzyme. This tautomer, although NLE calculations show it to have the most electrophilic carbon at the 8-position,¹¹⁰ has a debatable existence in this reaction. With 7-methylhypoxanthine, in which intramolecular hydrogen-bonding of this type cannot exist, oxidation occurs first at the 2-position. Similar configurational considerations may explain the fact that rat liver enzymes convert purine to uric acid¹¹¹ in the reverse order of oxidation to that obtained with xanthine oxidase, substitution occurring first at the 8- then at the 2- and 6-positions. There are indications, however, with some purines, that oxidation to the same product can occur simultaneously along two pathways at comparable rates.¹⁰⁴

The interrelationship between the 2- and 8-positions is exemplified by 2-oxo-¹⁰³ and 8-oxopurine, which are both converted by xanthine oxidase to 2,8-dioxopurine. Some unexpected results of oxidation can best be explained by assuming stereospecific factors. Thus, whereas purine, its 2-methyl, and its 2-amino derivatives give the 6-oxo derivatives, the 2-phenyl- and 2-oxopurines mentioned above oxidize at the 8-position.¹¹²

The effect of methylation of ring nitrogens upon the reactivity of

¹⁰⁹ F. Bergmann, H. Burger-Rachamimov, and M. Tamari, *Biochem. Biophys. Res. Commun.* **12**, 284 (1963).

¹¹⁰ A. M. Perrault, *J. Theoret. Biol.* **2**, 263 (1962).

¹¹¹ G. E. Jamison and M. P. Gordon, *Biochim. Biophys. Acta* **72**, 106 (1963).

¹¹² F. Bergmann, G. Levin, and H. Kwietny, *Biochim. Biophys. Acta* **30**, 509 (1958).

the purines toward enzymes is to slow down or stop completely, rather than alter, the course of the process. This result may be an indication that the methylated purines are unable to fit as close to the enzyme receptor surface as the parent purines. Consequently, if the stereospecific requirements are not satisfied, further oxidation is inhibited. The pathway can sometimes be unblocked by changing the enzyme system: 3-methylhypoxanthine can be converted to 3-methyluric acid, but the last oxidation step from the xanthine to a uric acid derivative requires replacement of the mammalian xanthine oxidase by one derived from a bacterial source.¹¹³ In contrast, both 7- and 9-methylpurine are readily oxidized to their hypoxanthine analogs but are resistant to further treatment,^{102, 103} as are the corresponding methylated xanthine homologs.

6. *Electrophilic Substitution at a Carbon Atom*

Electrophilic substitution is possible at either a carbon or a nitrogen atom. However, of the two sites, from both a chemical and a biological standpoint, the more important reactions involve the heteroatom. Of the five cyclic carbon atoms, only that at the 8-position shows pronounced nucleophilic character. Purine itself appears not to undergo electrophilic attack at this carbon, and the presence of at least one electron-releasing group is necessary to counteract the effect exerted on the π -electrons of the imidazole ring by the electron-attracting nature of the pyrimidine ring. Direct bromination¹¹⁴ of adenine and hypoxanthine to the 8-bromo derivatives is possible, the reaction also being successful with acetylated forms of the ribosides, adenosine, guanosine, and inosine.^{114a} The 8-position becomes more nucleophilic in dioxapurines and N-alkylated purines so that chlorination is possible.^{115, 116} Both caffeine and theobromine, on treatment with phosphoryl chloride-phosphorus pentachloride mixtures, undergo concurrent electrophilic and nucleophilic chlorination¹¹⁷ and give rise to the same product, 2,6,8-trichloro-7-methylpurine. Pyrimidine ring demethylation also occurs during the reaction.

Direct nitration, producing 8-nitropurines, has been successful only

¹¹³ S. Dikstein, F. Bergmann, and Y. Henis, *J. Biol. Chem.* **224**, 67 (1959).

¹¹⁴ M. Kruger, *Z. Physiol. Chem.* **61**, 329 (1892).

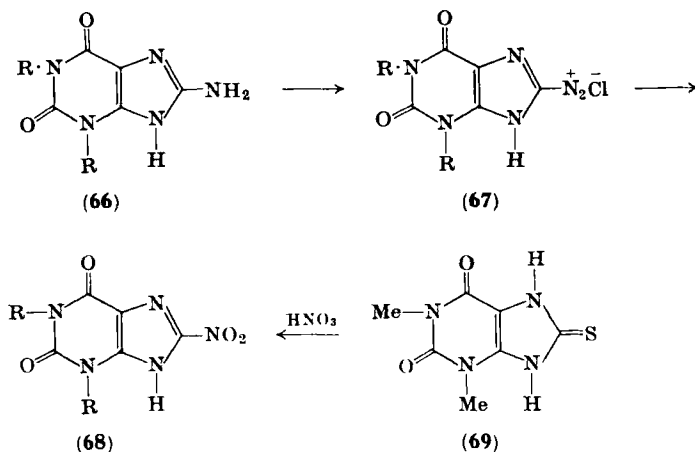
^{114a} R. E. Holmes and R. K. Robins, *J. Am. Chem. Soc.* **86**, 1242 (1964).

¹¹⁵ R. R. Adams and F. C. Whitmore, *J. Am. Chem. Soc.* **67**, 1271 (1945).

¹¹⁶ H. Biltz and E. Topp, *Ber. Deut. Chem. Ges.* **44**, 1524 (1911).

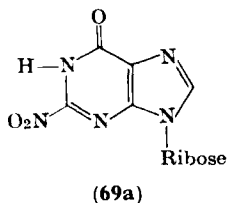
¹¹⁷ E. Fischer, *Ber. Deut. Chem. Ges.* **28**, 2480 (1895).

with methylated derivatives of xanthine.¹¹⁸⁻¹²¹ Under the same conditions, hypoxanthine, xanthine, guanine, and 2-aminopurine⁹⁴ are not nitrated, but their 8-nitro analogs (68) can be obtained from the 8-amino derivatives (66) by diazotization (67) and the action of



R = H or Me

nitrite ions.¹²¹ It is appropriate to mention here that a similar replacement of the 2-amino by a nitro group has been claimed.^{121a} The main product from the reaction of nitrous acid on guanosine was the expected xanthosine, but this was found to contain a small amount (5%) of material identified as 2-nitroinosine (69a). In view of the usual



¹¹⁸ B. F. Duesel, H. Berman, and R. J. Schachter, *J. Am. Pharm. Assoc.* **43**, 619 (1954).

¹¹⁹ H. Biltz and J. Sauer, *Ber. Deut. Chem. Ges.* **64**, 752 (1931).

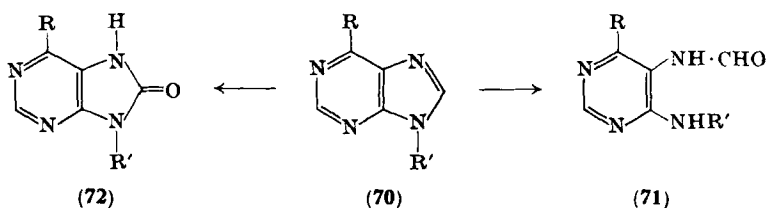
¹²⁰ H. Brunner and H. Leins, *Ber. Deut. Chem. Ges.* **30**, 2584 (1897).

¹²¹ J. W. Jones and R. K. Robins, *J. Am. Chem. Soc.* **82**, 3773 (1960).

^{121a} R. Shapiro, *J. Am. Chem. Soc.* **86**, 2948 (1964).

electron-deficient character of the 2-carbon atom, this reaction is proposed to occur via a nucleophilic substitution by nitrite ion of the diazonium group.^{121a} Another route (69→68) producing 8-nitropurines was initially considered to have given 8-nitrosopurines,¹¹⁹ but these were shown later to be mixtures of 8-nitropurines and starting material¹²¹; here an 8-thione group (69) undergoes electrophilic substitution by a nitronium ion.

That only N-methylated purines can be nitrated directly points to the strongly nucleophilic 8-carbon required, this condition needing groups in the rings capable of intensifying the electron-density in the imidazole ring. For reactions requiring a weaker nucleophilic carbon atom, such as coupling with alkali diazonium salts,^{122, 123} oxo- and aminopurines are sufficiently reactive to permit this to occur.



Free Radical Attack. One consequence of X-irradiation of biological material is the disruption of nucleic acid in the cell, the causative agent being the hydroxyl radicals formed under the conditions of the reaction.¹²⁴ Being electron-deficient, the radicals behave as very strong electrophiles and are capable of oxidation of the purine nuclei, leading to destabilization and bond-breaking of the nucleic acid. *In vitro* studies using X-rays or Fenton's reagent (hydrogen peroxide-ferrous salt) as source of radicals, have been made on aqueous solutions of purines and their nucleosides. If aerobic conditions are employed, the sequence of oxo substitution is that calculated using free valence indices,⁴⁹ the order being C-6, C-8, then C-2. Thus 2-aminopurine is converted to guanine¹²⁵ while 6-substituted purines (70) such as adenine and hypoxanthine undergo 8-oxidation (72).

¹²² J. P. Spies and T. H. Harris, *J. Am. Chem. Soc.* **61**, 351 (1939).

¹²³ L. F. Cavalieri and A. Bendich, *J. Am. Chem. Soc.* **72**, 2587 (1960).

¹²⁴ J. Weiss, *Nature* **153**, 748 (1944).

¹²⁵ C. Nofre, A. Lefier, and A. Cier, *Compt. Rend.* **253**, 687 (1961).

With oxygen-free atmospheres, attack at the 8-position is followed by degradation to 5-formamidopyrimidines (71).^{126, 127} The complexity of this reaction is shown by the fact that adenine gives, in addition to the 5-formamidopyrimidine, some 8-oxoadenine¹²⁸ and small amounts of hypoxanthine, produced by oxo displacement of the amino group.

7. Electrophilic Substitution at a Nitrogen Atom

In view of the π -electron-excessive character of the imidazole moiety, it is not surprising that electrophilic substitution occurs first at one of the nitrogens in this ring. Further attack is directed to a pyrimidine ring nitrogen. Adenine is the most important exception to this rule in undergoing pyrimidine ring alkylation first. As a generalization, alkylation at one site renders the molecule more amenable to secondary alkylation which usually takes place in the conjugate ring. Among the various electrophilic reagents employed, which are mainly the type that react by an S_N2 mechanism, are alkyl halides and sulfates, acyl halides, carbonium ions derived from unsaturated cyclic hydrocarbons, strained ring derivatives such as cyclic imines and epoxides, acid anhydrides, alkane sulfonates, and diazoalkanes. The extensive use of alkylating agents in the treatment of neoplastic diseases has led to *in vitro* and *in vivo* studies on the mode of action. It has been shown that in the nucleic acids of the cell the purines, especially guanine,¹²⁹ and the pyrimidines are major sites of attack.

Purine itself methylates only at the 9-position¹³⁰ with dimethyl sulfate or methanolic diazomethane, no 7-isomer being obtained. With mono-,²⁵ di-,^{60, 87} and trichloropurines,⁵⁴ alkaline dimethyl sulfate or methyl iodide gives mixtures of the 7- and 9-isomers. Even with alkylation by 3-bromocyclohexene,¹³¹ where steric factors may apply, both isomers are obtained with 6-chloropurine. Acid conditions also favor attack in the five-membered ring, where the 9-isomer is preferentially formed. When unsaturated cyclic ethers, such as

¹²⁶ G. Hems, *Nature* **185**, 525 (1960).

¹²⁷ G. Hems, *Nature* **181**, 1721 (1958).

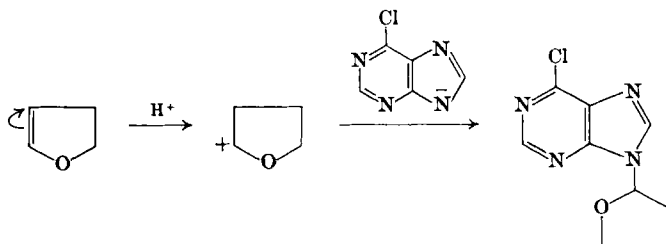
¹²⁸ C. Ponnampuruma, R. M. Lemmon, and M. Calvin, *Radiation Res.* **18**, 540 (1963).

¹²⁹ P. Brookes and P. D. Lawley, *Biochem. J.* **77**, 478 (1960).

¹³⁰ H. Bredereck, H. Ulmer, and H. Waldman, *Ber.* **89**, 12 (1956).

¹³¹ H. J. Schaeffer and R. D. Weimar, *J. Am. Chem. Soc.* **81**, 197 (1959).

dihydrofuran¹³² or dihydropyran,¹³³ are used, acid is present and the actual alkylating agent is the protonated form (Scheme 3) which reacts with the purine. This reaction, which has also been used to 9-substitute 2,6-dichloro-¹³⁴ and 2,6,8-trichloropurines,⁶¹ fails if electron-releasing groups such as amino or thione are present. The base-strengthening effect of these groups presumably lowers the concentration of purine-free base, but this can be overcome, as was done in the case of 2-amino-6-chloropurine by conversion to 2-acetamido-6-chloropurine.¹³⁴



SCHEME 3

The behavior shown by purinones toward alkylating agents illustrates well how the reaction pathway is governed by the choice of reagent and the conditions employed. With alkaline methyl iodide or dimethyl sulfate, for example, methylation follows the order N-3, N-7, then N-1,¹³⁵ but if neutral or acid conditions prevail, both N-7 and N-9, i.e., the imidazole nitrogens, are substituted and betaine structures (Scheme 4) are obtained.^{76, 136} Neutral conditions are provided by use of aprotic solvents such as dimethylsulfoxide or dimethylacetamide. A number of *N*-methylxanthines¹³⁷ and purines with 6-oxo⁷⁶ and 6-alkylthio¹³⁸ groups have been quaternized in this way. The presence of potentially tautomeric groups does not appear

¹³² L. R. Lewis, F. H. Schneider, and R. K. Robins, *J. Org. Chem.* **26**, 3837 (1961).

¹³³ R. K. Robins, E. F. Godefroi, E. C. Taylor, L. R. Lewis, and A. Jackson, *J. Am. Chem. Soc.* **83**, 2574 (1961).

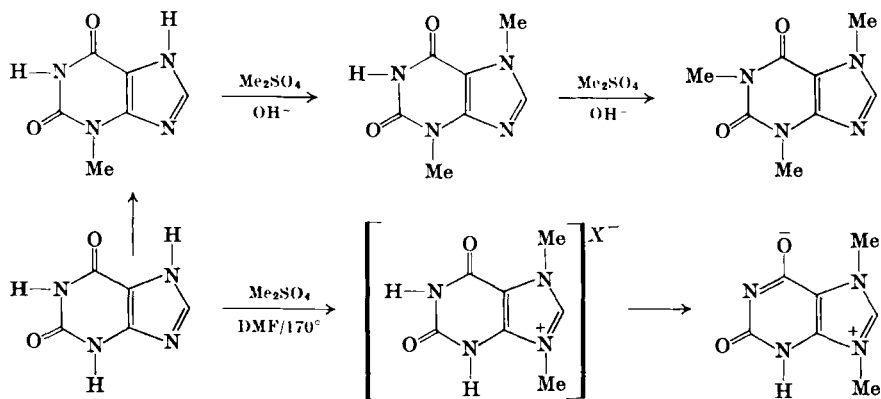
¹³⁴ W. A. Bowles, F. H. Schneider, L. R. Lewis, and R. K. Robins, *J. Med. Pharm. Chem.* **6**, 471 (1963).

¹³⁵ H. Brederick, K. von Schuh, and A. Martini, *Ber.* **83**, 201 (1950).

¹³⁶ W. Pfeleiderer, *Ann.* **647**, 161 (1961).

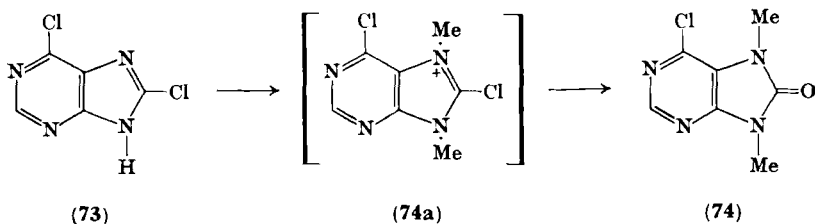
¹³⁷ H. Brederick, O. Christmann, W. Koser, P. Shellenberg, and R. Nast, *Ber.* **93**, 1812 (1962).

¹³⁸ W. P. Pfeleiderer, *Ann.* **647**, 167 (1961).



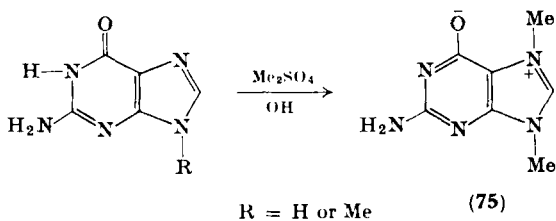
SCHEME 4

necessary for the reaction to occur, as 6,8-dichloropurine (73) in dimethylsulfoxide can be quaternized⁶⁰ but the derivative isolated is 6-chloro-7,9-dimethylpurin-8-one (74). Hydrolysis of the chlorine atom at the 8-position of the intermediate (74a) seems to take place



during the aqueous conditions used in the isolation procedure and is facilitated by the increased electrophilicity of the 8-carbon induced by the positive charge of the quaternary form.

The naturally occurring¹³⁸ dimethyl derivative of guanine (75), herbipoline, is obtained when guanine or its 9-methyl homolog is



methylylated.¹³⁹ This betaine is of interest in being a model compound for the products arising from the alkylation of guanylic and deoxyguanylic acids.^{140, 141} Such 7-alkylated ribosides are acid- and alkali-labile but, whereas acid media lead to fission of the N-9—C-10 glycosidic link and the production of 7-methylguanine¹⁴¹ (Scheme 5), alkaline conditions cause hydroxyl ion attack at the 8-carbon with a resulting opening of the imidazole ring. These reactions offer a mechanism for the disruption of nucleic acids which occurs *in vivo* after exposure of the organism to alkylating agents.¹⁴²

The 7-nitrogen in guanine derivatives is the most nucleophilic,^{137, 141, 143} but the 1-position in guanosine is methylated when methyl iodide in dimethylsulfoxide^{143a} is used in the presence of potassium carbonate. One group, after treating aqueous solutions of guanosine with diazomethane, claimed¹⁴⁴ to have prepared the 1-methyl homolog but the product has been shown to be 7-methylated guanosine.^{144a} Similarly, the attempted preparation of 1-methylguanine-9-deoxyriboside,¹⁴⁵ using this reagent, may have given rise to the 1,7-dimethylated product.^{143a} However, it should be noted that, under these conditions, hypoxanthine^{145a} and adenine ribosides¹⁴⁶ will form 1-*N*-methyl derivatives, with some N-7 and O-methylation occurring with the former. The $-I$ effect of the ribose moiety undoubtedly enhances the acidic dissociation of the proton at N-1, as does quaternization in the betaines.¹⁴⁷

The sulfur-containing analogs of the oxopurines, because of the greater nucleophilicity of sulfur, will alkylate on either nitrogen or sulfur. Aqueous media dispose toward S-alkylation, whereas aprotic solvents are more likely to lead to nuclear alkylation. For example,

¹³⁹ D. Ackerman and P. H. List, *Z. Physiol. Chem.* **309**, 286 (1957).

¹⁴⁰ P. D. Lawley, *Proc. Chem. Soc.* **1957**, 290.

¹⁴¹ P. Brookes and P. D. Lawley, *J. Chem. Soc.* **1961**, 3923.

¹⁴² G. P. Warwick, *Cancer Res.* **23**, 1315 (1963).

¹⁴³ H. Bredereck, H. Heise, O. Christmann, and P. Shellenberg, *Angew. Chem., Intern. Ed. Engl.* **1**, 159 (1962).

^{143a} A. D. Broom, L. B. Townsend, J. W. Jones, and R. K. Robins, *Biochemistry* **3**, 494 (1964).

¹⁴⁴ H. Bredereck, *Ber.* **80**, 401 (1947).

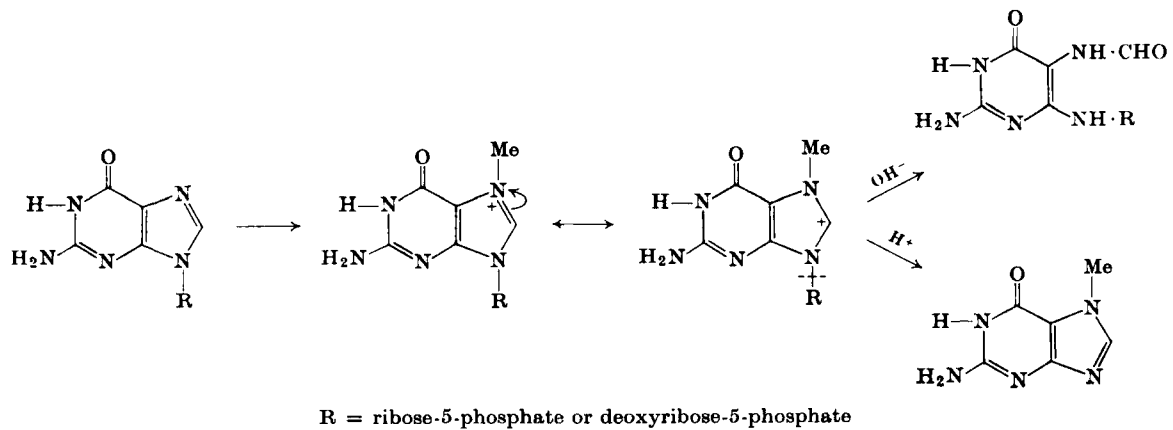
^{144a} J. A. Haines, C. B. Reese, and A. R. Todd, *J. Chem. Soc.* **1962**, 5281.

¹⁴⁵ O. M. Friedman, G. N. Mahapatra, and R. Stevenson, *Biochim. Biophys. Acta* **68**, 144 (1963).

^{145a} H. T. Miles, *J. Org. Chem.* **26**, 4761 (1961).

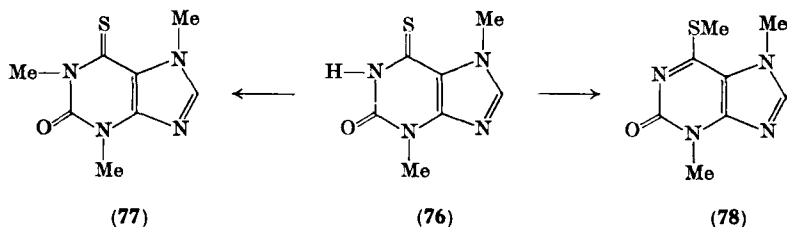
¹⁴⁶ J. A. Haines, C. B. Reese, and A. R. Todd, *J. Chem. Soc.* **1964**, 1406.

¹⁴⁷ P. D. Lawley and P. Brookes, *Biochem. J.* **92**, 19c (1964).

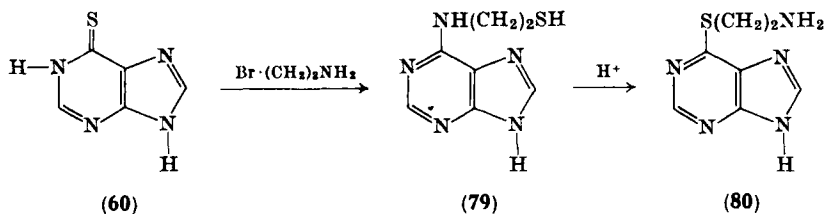


SCHEME 5

under alkaline conditions, 1-methylpurine-6-thione with a benzyl halide gives the S-benzyl derivative, whereas in dimethylformamide the 7-benzyl isomer is obtained.^{76, 148} This result contrasts with that obtained from the same treatment of 1-methylhypoxanthine which gave the 9-benzylpurine.⁹⁰ However, aprotic solvents do not always preclude S-alkylation, as benzylation of 3-benzylpurine-6-thione leads



to the S-benzylated form. If 3-benzylhypoxanthine is used, the product is the 7-benzylated purine, rather than the 9-isomer. In this case steric considerations due to the proximity of the 3-benzyl group may preclude occurrence of 9-benylation.⁹⁰ Generally speaking, conditions which N-alkylate also S-alkylate, but milder conditions favor substitution on the sulfur atom, for more vigorous conditions



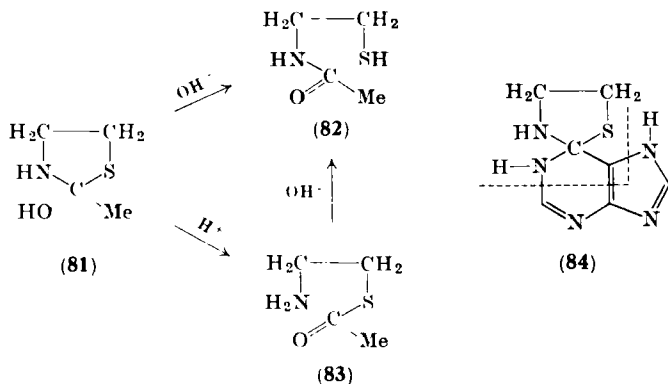
will dealkylate S-alkylpurines. This explains the failure to obtain 6-methylthiotheobromine (78) from 6-thiotheobromine (76) with alkaline methyl sulfate at 40°, the reaction giving only the 1-methylated derivative (77). With methyl iodide¹⁴⁹ at lower temperature, however, the S-alkylated derivative (78) is formed.

An anomalous result arose from the alkylation of purine-6-thione with 2-bromoethylamine. The product was not the S-alkylated purine (80) but the adenine derivative (79) which, on acid treatment, reverted

¹⁴⁸ L. B. Townsend and R. K. Robins, *J. Org. Chem.* **27**, 990 (1962).

¹⁴⁹ K. R. Wooldridge and R. Slack, *J. Chem. Soc.* **1962**, 1863.

to the required S-alkylated purine¹⁵⁰ (**80**). A rearrangement of this type can be explained by drawing an analogy with N→S acyl group migrations which occur in the peptide field.¹⁵¹ An intermediate structure of the type **84** can be compared with the product (**81**) formed by addition of water across the double bond of 2-hydroxy-2-methylthiazolidine.¹⁵² This type of cyclic structure, according to the pH conditions adopted, ring-opens to either the N-acyl (**82**) or S-acyl (**83**) derivative. Stronger acid treatment of **80** gives the tricyclic derivative (**86**) by an unspecified mechanism involving the quaternary salt (**85**). It is pertinent to note that other simple quaternary alkylammonium hydroxides have been used as alkylating agents, giving rise to 1-, 7-, and 9-alkylpurines.¹⁵³



Dihydrothiazolopyrimidines of type **86** can be prepared directly by a two-stage alkylation of 6-mercaptapurines with 1,2-dihaloalkanes; the 2-haloethylpurine (**87**, R = halogen) initially formed under mild conditions, undergoes endoalkylation to **86**.¹⁵⁴ Dihydrothiazoles of this type possess a labile C-8—S-9 bond susceptible to nucleophilic attack, sulfide ions giving derivatives of 1-substituted purine-6-thione¹⁵⁵ (**88**). Hydroxyl ions will normally attack 6-alkylmercapto-

¹⁵⁰ T. P. Johnston and A. Gallagher, *J. Org. Chem.* **28**, 1305 (1963).

¹⁵¹ T. Wieland, E. Bokelmann, L. Bauer, H. V. Lang, and H. Lau, *Ann.* **583**, 129 (1953).

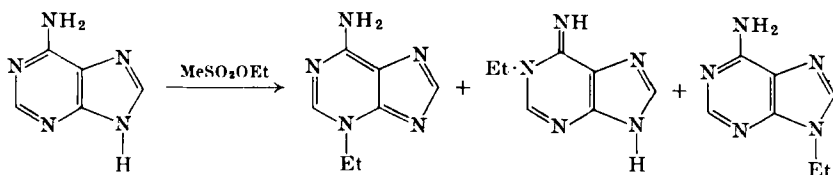
¹⁵² K. Linderström-Lang and C. F. Jacobsen, *J. Biol. Chem.* **137**, 443 (1941).

¹⁵³ T. C. Myers and L. Zeleznick, *J. Org. Chem.* **28**, 2087 (1963).

¹⁵⁴ R. W. Balsiger, A. L. Fikes, T. P. Johnston, and J. A. Montgomery, *J. Org. Chem.* **26**, 3446 (1961).

¹⁵⁵ J. A. Montgomery, R. W. Balsiger, A. L. Fikes, and T. P. Johnston, *J. Org. Chem.* **27**, 195 (1962).

exocyclic amino group occurs, more forcing conditions being necessary. The same three positions are alkylated in 6-substituted aminopurines,¹³ but under strongly basic conditions benzyl chloride gives a mixture of 7- and 9-benzyl-6-dimethylaminopurines.¹⁶⁰ Use of aprotic solvents does not promote betaine formation, i.e., 7,9-dimethylation, as with hypoxanthine and guanine, but the main product is the 3-alkylated adenine^{76,161,162} with traces of the 1- and 9-alkyl derivatives.¹⁶³ Further alkylation of 3-substituted adenine is directed to the 7-nitrogen, thus affording a convenient route to 7-alkyladenines by direct alkylation, if an easily removable group, e.g., benzyl, is



SCHEME 6

already present at the 3-position.¹⁶³ Alkylation of 7-alkyladenine also gives 3,7-dialkyladenine.¹⁶³ Replacement of the imidazole proton, as in 9-methyladenine, promotes the 1-nitrogen to the most nucleophilic center and also slightly activates the 7-position. Use has been made^{163a} of this to prepare 1-substituted adenines, starting with 9-benzyladenines, the procedure paralleling that adopted above for the 3-substituted adenines. If the 1-position is substituted, then alkylation occurs at the 9-position. This correspondence of the 1- and 9-positions toward alkylation is the same as found between the 3- and 7-positions, i.e., substitution at one site of the pair directs alkylation to the other one. Adenosine and the deoxyribosyl analog,¹⁶⁴ in which the 9-positions are blocked by the sugar group, give 1-methyladenosine and a little of the 3-isomer.¹⁶ Adenosine, like guanosine, is attacked by diazomethane at the most nucleophilic center, giving the 1-methyl derivative.¹⁴⁶ Under acid conditions, ethylene oxide will quaternize adenosine on the 1-position (91), the product rearranging in alkali,

¹⁶⁰ B. R. Baker, R. E. Schaub, and J. P. Joseph, *J. Org. Chem.* **19**, 643 (1954).

¹⁶¹ J. A. Montgomery and H. J. Thomas, *J. Am. Chem. Soc.* **85**, 2672 (1963).

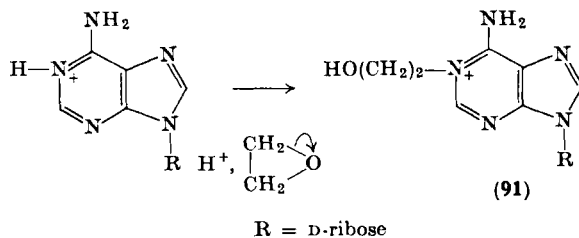
¹⁶² N. J. Leonard and J. A. Deyrup, *J. Am. Chem. Soc.* **84**, 2151 (1962).

¹⁶³ N. J. Leonard and T. Fuji, *J. Am. Chem. Soc.* **85**, 3719 (1963).

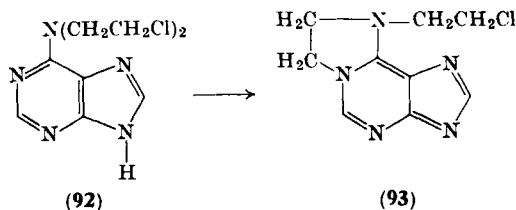
^{163a} N. J. Leonard and T. Fuji, *Proc. Natl. Acad. Sci. U.S.* **51**, 73 (1964).

¹⁶⁴ A. Coddington, *Biochim. Biophys. Acta* **59**, 472 (1962).

like other 1-alkyladenines, to a 6-alkylaminopurine.⁹⁷ The facility with which the 1-position alkylates prevents isolation of nitrogen mustard-bearing purines of the type **92**, which spontaneously cyclizes to the dihydroimidazole (**93**).¹⁶⁵ The unchanged spectra over the whole pH range demonstrates the fixed bond structure.



Acetylation has been studied in a few purines and is generally found to take place in the imidazole ring, though extranuclear groups may also be affected. Adenine forms a diacyl derivative which is easily hydrolyzed to the monoacetylated adenine.^{166,167} The more labile group is located on an imidazole nitrogen, with the other comprising a 6-acetamido group. Both amino groups in 2,6-diaminopurine as well



as the imidazole nitrogen are acetylated. The acetyl group on the five-membered ring is removed with hot water and is assigned to the 9-position.⁸⁸ Purine itself gives almost equal amounts of the 7- and 9-acetylurine,¹⁶⁸ the 7-position being more favored. With 6-methylpurine only the 9-acetylurine is obtained; steric hindrance may prevent formation of the 7-isomer. Lack of physical data prevents any conclusions to be drawn as to the factors which govern whether the

¹⁶⁵ T. P. Johnston, A. L. Fikes, and J. A. Montgomery, *J. Org. Chem.* **27**, 973 (1962).

¹⁶⁶ L. Birkofer, *Ber.* **76**, 769 (1943).

¹⁶⁷ A. H. Schein, *J. Med. Pharm. Chem.* **5**, 303 (1962).

¹⁶⁸ G. S. Reddy, L. Mandell, and J. H. Goldstein, *J. Chem. Soc.* **1963**, 1414.

7- or 9-nitrogen is acetylated, but some NMR studies have been made.¹⁶⁸ Other acylating agents behave as above,¹⁶⁹ but purine-6- and -8-thiones are S-acylated,¹⁷⁰ these derivatives being analogous to those formed by the action of alkylating agents on purinethiones.

ACKNOWLEDGMENT

The author wishes to acknowledge, with thanks, the helpful advice given by Professor Adrien Albert during the preparation of this manuscript.

¹⁶⁹ E. Dyer, J. M. Reitz, and R. E. Farris, *J. Med. Pharm. Chem.* **6**, 298 (1963).

¹⁷⁰ E. Dyer and H. S. Bender, *J. Med. Pharm. Chem.* **7**, 10 (1964).

The Reduction of Nitrogen Heterocycles with Complex Metal Hydrides

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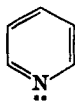
PAUL S. ANDERSON

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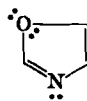
The reactions of complex metal hydrides occur by an attack of the nucleophilic hydride ion on an electrophilic center.¹ Aromatic nitrogen heterocycles in which the nitrogen has contributed only one electron to the π -system (**1**) are electrophilic as compared with benzene, and have been shown to undergo reduction by the active reducing agent, lithium aluminum hydride. The nitrogen heterocycles in which the heteroatom has contributed two electrons to the π -system (**2**) are electron-rich as compared with benzene and usually do not undergo reaction by reduction with complex metal hydrides.² A combination of these two structural features, as in oxazoles (**3**), usually induces sufficient electrophilicity to allow attack by the hydride ion and reduction.



(1)



(2)



(3)

Compounds having the bonding of type **1** retain the basicity of the nitrogen, and formation of quaternary salts of these compounds increases the electrophilicity of the ring. Such quaternary salts are therefore highly reactive to metal hydrides and undergo reduction with the less reactive hydrides. This chapter will attempt to provide sufficient examples of the various types of nitrogen heterocycles which have been investigated to provide a basis for evaluating this method of reduction in the synthesis of reduced and partially reduced nitrogen heterocycles.

I. Mechanism

The mechanistic aspects of this reaction have been more extensively investigated with pyridine and pyridinium salts than with other

¹ N. G. Gaylord, "Reduction with Complex Metal Hydrides." Wiley (Interscience), New York, 1955.

² A. R. Katritzky and J. M. Lagowski, "Heterocyclic Chemistry," p. 69. Wiley, New York, 1960.

systems, but the correlations derived from these studies should be applicable to other heterocycles. Because of the relative reactivity of the metal hydrides and the solubility properties of the nitrogen heterocycles and hydrides, lithium aluminum hydride or a similar reagent is effective with the amines, and sodium borohydride with the amine salts. The former reaction most often leads to dihydropyridines, whereas the latter reaction gives predominantly tetrahydropyridines. Because of the greater complexity of the reduction of pyridinium salts with sodium borohydride, this reaction will be considered in detail. The reduction of the pyridinium moiety of the coenzyme, nicotinamide adenine dinucleotide, with sodium borohydride gave a dihydropyridine unlike that in the natural reduced coenzyme (a 1,4-dihydropyridine).^{3,4} This discovery generated an interest in the reduction which was shown by numerous subsequent workers to lead to dihydropyridines, 1,2,3,6-tetrahydropyridines, and occasionally piperidines, depending upon the conditions of the reduction and the structure of the pyridinium ion.

The pyridinium salts have been shown to have electrophilic positions at the 2-, 4-, and 6-carbon atoms. Of these, the 2- and 6-positions should be the more positive because of the proximity to the quaternary nitrogen. From the ultraviolet absorption spectra of the reaction mixtures during the reduction and of the isolated products, it can be demonstrated that the predominant attack of the hydride ion from sodium borohydride occurs at these two positions.^{5,6} The 1,6-dihydropyridine (such as **5**) formed from the reduction of a 1,3-disubstituted pyridinium ion appears to be stable toward further reduction, for a number of such compounds have been isolated from sodium borohydride reductions containing sufficient borohydride to complete the reduction to the tetrahydro-state.⁷⁻¹⁰ Since 1,4-dihydropyridines having a 3-substituent which is electron-withdrawing have also been

³ M. B. Mathews, *J. Biol. Chem.* **176**, 229 (1948).

⁴ M. B. Mathews and E. E. Conn, *J. Am. Chem. Soc.* **75**, 5428 (1953).

⁵ D. A. Nelson, Thesis, University of New Hampshire, Durham, 1960.

⁶ K. Wallenfels and H. Schöly, *Ann.* **621**, 215 (1959).

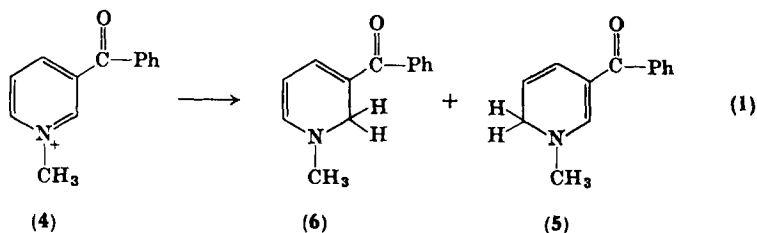
⁷ K. Schenker and J. Druey, *Helv. Chim. Acta* **42**, 1960 (1959).

⁸ N. Kinoshita, M. Hamana, and T. Kawasaki, *Chem. Pharm. Bull. (Tokyo)* **10**, 753 (1962).

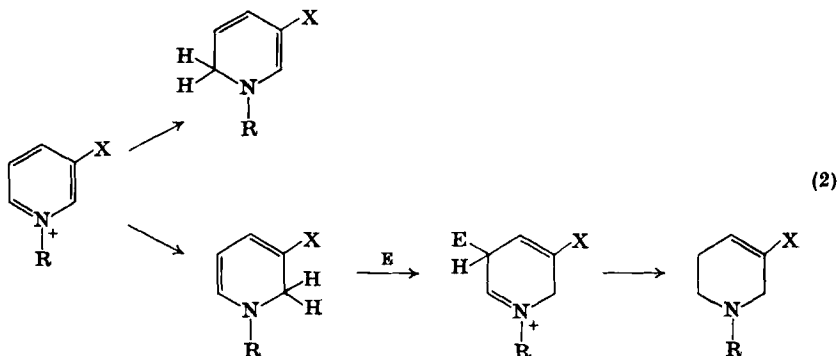
⁹ N. Kinoshita, M. Hamana, and T. Kawasaki, *Yakugaku Zasshi* **83**, 115 (1963).

¹⁰ N. Kinoshita and T. Kawasaki, *Yakugaku Zasshi* **83**, 120, 123, and 126 (1963).

shown to be stable to borohydride reduction, the intermediate dihydropyridine in the formation of the 1,2,5,6-tetrahydropyridines was evidently a 1,2-dihydropyridine such as **6**. This could be demonstrated by following the changes in the ultraviolet absorption spectrum of the 1-methyl-3-benzoylpyridinium ion (**4**) which occurred during the reduction with sodium borohydride (Eq. 1).⁵ The long wavelength maximum (475–490 m μ) resulting from the 1,2-dihydropyridine **6** increased rapidly in intensity and then slowly diminished,



whereas the shorter wavelength maximum (388 m μ) due to the 1,6- (or 1,4)-dihydropyridine maintained approximately the same intensity regardless of the length of reaction time. This observation strongly supported the postulated mechanism of Katritzky¹¹ for the formation of the tetrahydropyridines, i.e., the attack of an electrophile on the dienamine system of the dihydropyridine with subsequent reduction of the immonium salt thus formed (Eq. 2):

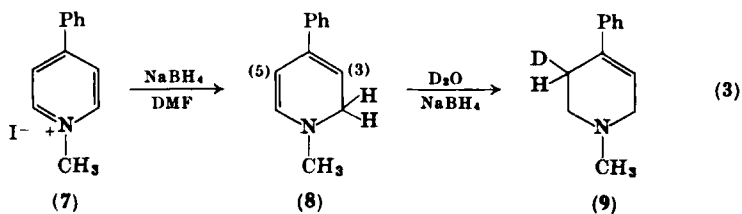


The electrophile (E) which attacks the dienamine system could be a proton from the solvent (water or alcohol) or borane formed from the

¹¹ A. R. Katritzky, *J. Chem. Soc.* **1955**, 2586.

borohydride. The comparable reduction of the dienamine, cholestene enamine, was originally proposed to occur by intermediate attack of borane; however, this pathway has now been discarded.¹² The borane attack seems unlikely in the case of the dihydropyridines, for diborane should undergo reaction with the solvent in preference to reaction with the dienamine system. The dihydropyridines have been shown to be stable in diglyme and dimethylformamide until a proton source was added, and the organo-borane which would be formed by the borane attack would not be expected to undergo hydrolysis of the boron-carbon bond under the conditions of the isolation of the product. Kawasaki and co-workers, however, still support this mechanism on the basis of the stoichiometry of the reaction, the isolation of the 1,2-dihydropyridine from the reduction of methyl nicotinate methiodide with sodium borohydride in methanolic base, and reduction of the 1,2-dihydropyridine by excess diborane.⁸⁻¹⁰

The direct attack of proton from the solvent on the intermediate dihydropyridine as well as the over-all mechanism of the reduction received support from the extent and position of deuterium labeling in the product from the reduction of 1-methyl-4-phenyl-pyridinium iodide (7) with sodium borohydride in dimethylformamide and deuterium oxide. The 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (9) formed was shown by nuclear magnetic resonance (NMR) and mass spectral analysis to contain approximately one deuterium atom located at the 3-position.^{13,14} This is the result to be expected from the pathway shown in Eq. (3) if the electrophile were a deuterium.



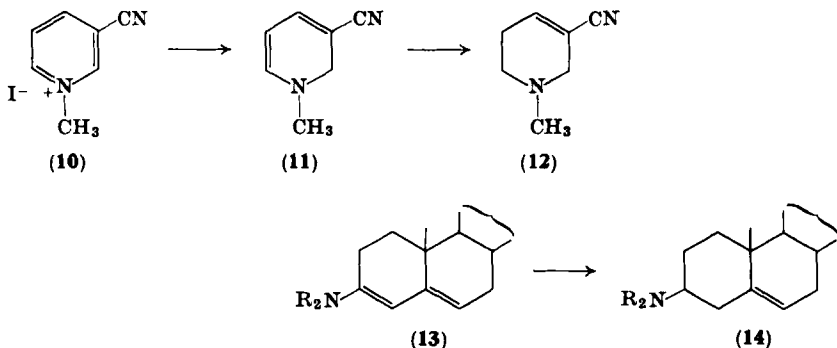
The attack of the electrophile on the dienamine system could occur at the terminal carbon of the central double bond (5-position) or at

¹² J. A. Marshall and W. S. Johnson, *J. Org. Chem.* **28**, 421 (1963).

¹³ R. E. Lyle, D. A. Nelson and P. S. Anderson, *Tetrahedron Letters* No. 13, 553 (1962).

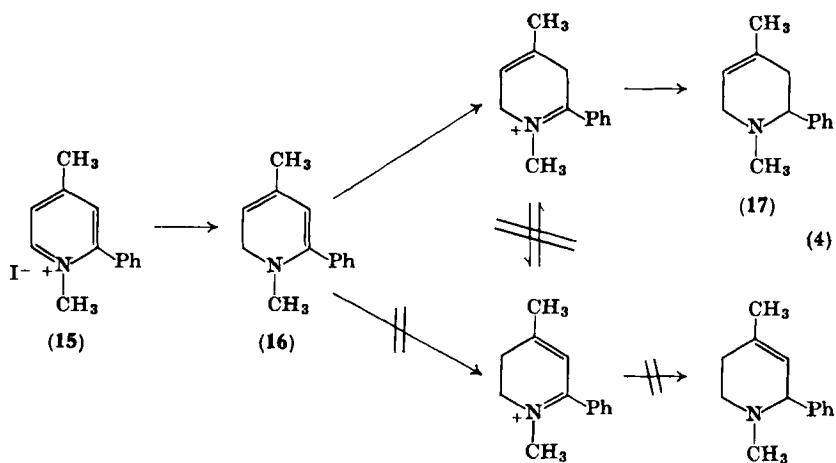
¹⁴ R. E. Lyle, P. S. Anderson, C. K. Spicer, S. S. Pelosi, and D. A. Nelson, *Angew. Chem.* **75**, 386 (1963).

the end of the dienamine system (3-position) in structure **8** (Eq. 3). A distinction between these two possibilities could not be made using the symmetrically substituted 1-methyl-4-phenylpyridinium iodide (**7**); however, the formation of 1-methyl-1,2,5,6-tetrahydronicotinonitrile (**12**) from the reduction of 1-methyl-3-cyanopyridinium iodide (**10**),

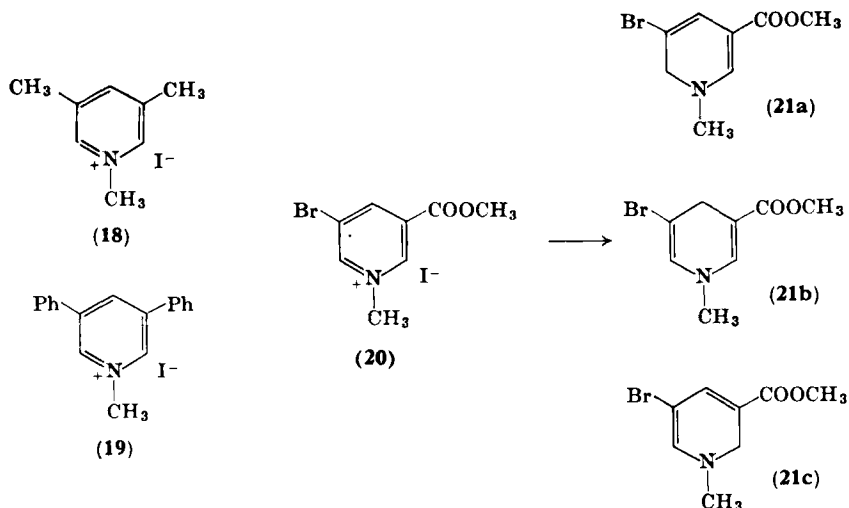


presumably via a 1,2-dihydropyridine intermediate (**11**),⁷ as well as the formation of 3-dimethylamino- Δ^5 -cholestene (**14**) from the reduction of cholestenone enamine (**13**),¹² strongly suggested that the electrophile attacked the center of the dienamine system.

Support for the above pathway was obtained by isolation and structure determination of the single product from the reduction of



1,4-dimethyl-2-phenylpyridinium iodide (**15**) with sodium borohydride. The intermediate dihydropyridine was shown to be 1,4-dimethyl-2-phenyl-1,6-dihydropyridine (**16**). This intermediate on protonation and further reduction gave 1,4-dimethyl-2-phenyl-1,2,3,6-tetrahydropyridine (**17**) as the only product. This product could arise only by the attack of the proton at the central double bond of the dienamine (Eq. 4) since the deuterium-labeling experiment described above eliminated any possibility of equilibration of the immonium isomers prior to reduction.¹⁵ Thus the protonation of dienamines seems to be correlated by the rule developed by Ingold for the protonation of the anion of α,β -unsaturated esters.^{15a}



The initial borohydride ion and proton attack seem to be subject to steric interference. 2-Substituted pyridinium ions form intermediate 1,6-dihydropyridines, and 3,5-disubstituted pyridinium ions are resistant to reduction past the dihydropyridine stage. The reduction of 1,3,5-trimethylpyridinium iodide (**18**) rapidly forms an intermediate dihydropyridine on reaction with sodium borohydride in alcohol; however, the conversion to the tetrahydropyridine is much slower than that observed for 2-, 4-, or 6-substituted pyridinium ions.

¹⁵ P. S. Anderson and R. E. Lyle, *Tetrahedron Letters* No. 3, 153 (1964).

^{15a} C. K. Ingold, "Structure and Mechanism in Organic Chemistry", p. 565, Cornell University Press, Ithaca, N.Y. 1953.

The reduction of 1-methyl-3,5-diphenylpyridinium iodide (**19**) and methyl 1-methyl-3-bromo-5-methoxycarbonylpyridinium iodide (**20**) gave mixtures of dihydropyridines (**21a,b,c**) which were resistant to further reduction, indicating that proton attack did not occur.^{16,16a}

The formation of piperidines from the borohydride reduction of pyridine and picoline methiodides has been reported by Ferles.¹⁷ He assumed that this complete reduction arose from initial formation of the 1,4-dihydropyridine, and that the ratio of tetrahydropyridine to piperidine represented the ratio of attack of hydride at the 2-position to that at the 4-position.

Piperidines have not been reported as products in the numerous other reductions; however, the products of 4-unsubstituted pyridinium ions definitely contain piperidines as shown by gas chromatographic analysis. The amount of the substituted piperidine can be related directly to the degree of steric interference to attack of the borohydride ion at the 2- or 6-positions, and thus by inference the completely saturated rings must be formed from 1,4-dihydropyridine intermediates¹⁶ (Eq. 5 and Table I).

TABLE I
REDUCTION OF 1-ALKYLPYRIDINIUM IONS

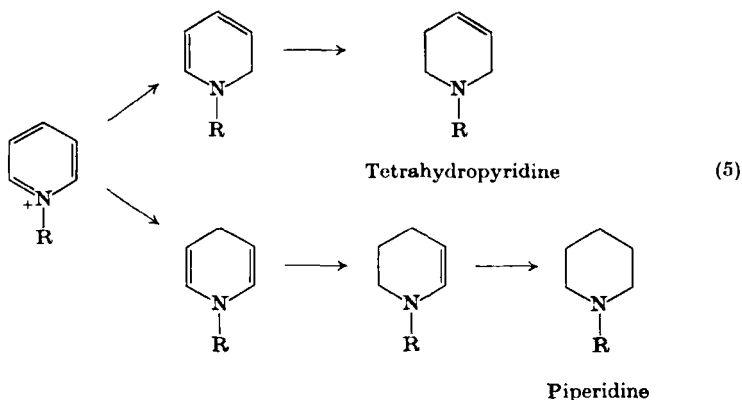
| R | Approximate yield (%) of: | |
|-----------------|---------------------------|------------|
| | Tetrahydropyridine | Piperidine |
| <i>n</i> -Butyl | 95 | 5 |
| Benzyl | 88 | 12 |
| Isopropyl | 72 | 28 |

The attack of the borohydride ion at the 4-position of pyridinium ions can be proved in the few instances in which the 1,4-dihydropyridines have been isolated. The dihydropyridine formed by the sodium or potassium borohydride reduction of 1-phenylpyridinium chloride (**22**) was shown to be a mixture of 20% 1,4- and 80% 1,2-

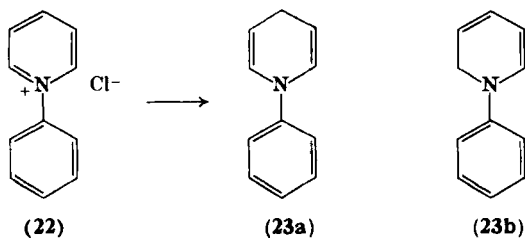
¹⁶ P. S. Anderson, Thesis, University of New Hampshire, Durham, 1963.

^{16a} See also K. Pollak, A. A. Hyatt, and O. Friedman, Abstracts of the 149th Meeting of the American Chemical Society, Detroit, Michigan, April, 1965, p. 9N.

¹⁷ M. Ferles, *Collection Czech. Chem. Commun.* **23**, 479 (1958).



dihydropyridines (**23a** and **b**). The bulk of the phenyl group interfered with attack of the borohydride ion at the 2- (6-) position sufficiently to cause competitive attack at the 4-position. The intermediate dihydropyridines would be less liable to proton attack than their 1-alkyl analogs since the orbital of the lone-pair of electrons on the nitrogen overlaps with the phenyl π -system as well as the enamine double bonds.¹⁸ Evidence for the presence of 1,4-dihydropyridines in the sodium borohydride reduction products of 3,5-disubstituted pyridine methiodides (cf. p. 52) was demonstrated by the NMR spectra of the product mixtures. These dihydropyridine isomers could be separated by thin-layer chromatography.¹⁶



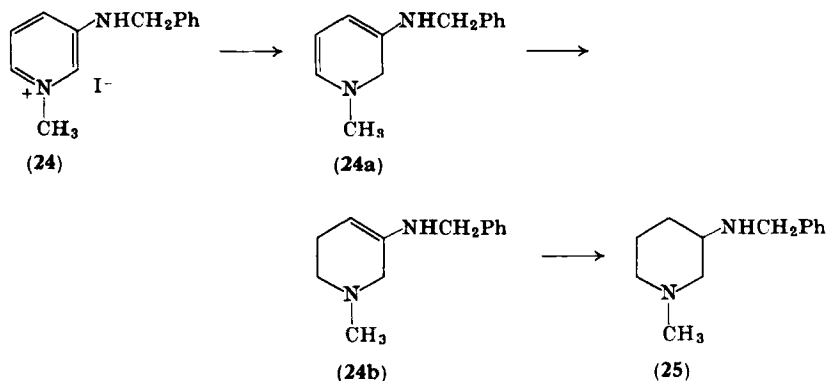
The following correlations developed from the sodium borohydride reductions of pyridinium ions can be extended to explain the products of reduction of the other nitrogen heterocycles:

- a. The attack of the hydride ion will occur at the carbon atom adjacent to the quaternary nitrogen if steric interferences do not occur.

¹⁸ M. Saunders and E. H. Gould, *J. Org. Chem.* **27**, 1439 (1962).

- b. The dienamine (or enamine) system thus formed will undergo attack by a proton from the solvent at the 3-position of the dienamine (or enamine) system provided that the nitrogen lone-pair of electrons is in an orbital overlapping only with the π -bonds of the dienamine (or enamine) system, and also provided that there is no substituent located at this 3-position.
- c. The attack of the borohydride ion and the proton are sensitive to steric interactions. Thus attacks will not occur at substituted positions or will occur only at a greatly reduced rate. Large substituents near the point of potential attack will direct attack to more distant positions.
- d. Reduction in strong base prevents protonation, and the dihydropyridines are stable.

The application of these correlations to the reduction of 3- and 4-aminopyridinium salts to aminopiperidines¹⁹ and the conversion of *p*-phenanthroline to the dihydro-derivative²⁰ will serve as illustrations. The reaction of 1-methyl-3-benzylaminopyridinium iodide (**24**)



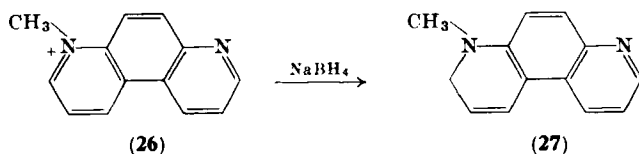
with the borohydride ion would be expected to occur by hydride attack at the 2-position. The 1,2-dihydropyridine (**24a**) would then undergo attack by proton and subsequently by borohydride to form 1-methyl-3-benzylamino-1,2,5,6-tetrahydropyridine (**24b**), but this intermediate also contains an enamine system involving the 3-benzylamino substituent. Thus a tautomeric shift of hydrogen to form the

¹⁹ G. N. Walker, M. A. Moore, and B. N. Weaver, *J. Org. Chem.* **26**, 2740 (1961).

²⁰ P. Karrer, M. Hubmann, and W. Traber, *Helv. Chim. Acta* **43**, 265 (1960).

imine or the similar proton attack on the enamine system would lead to a third attack by borohydride ion to give the hexahydro-product (25). Similar explanations can be given for the steps to form the 4-aminopiperidine.

The phenanthroline salt (26) would be attacked by the borohydride ion preferentially at the unsubstituted position adjacent to the quaternary nitrogen. The dienamine thus formed would be resistant to attack by a proton from the solvent because one of the double bonds of the system is a part of the remaining aromatic system, and protonation would disrupt the aromatic π -orbitals. Furthermore, the preferred position of attack by the proton is substituted and would not be subject to facile reaction. Thus the dihydro-derivative (27) formed by the initial attack would be stable.

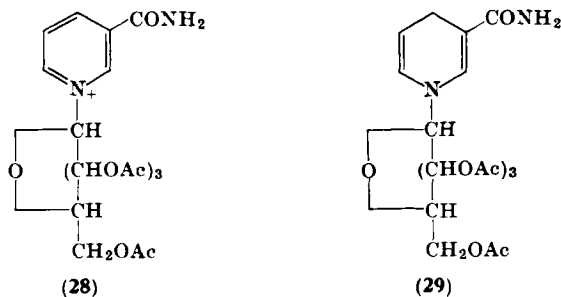


II. Reductions of Pyridines and Pyridinium Ions

A. REDUCTION OF PYRIDINIUM IONS BY SODIUM BOROHYDRIDE^{20a}

1. Formation of Dihydropyridines

The earliest investigation of the reduction of pyridinium ions with sodium borohydride was reported by Mathews³ on nicotinamide adenine dinucleotide. This reaction produced a dihydropyridine



^{20a} The reduction of a pyridine by sodium borohydride was reported by J. Kuthan and E. Janečková, *Collection Czech. Chem. Commun.* **29**, 1654 (1964).

exhibiting less than 50% of the coenzymatic activity of the natural reduced coenzyme. Panouse^{21, 22} shortly afterward described a more extensive study of the reduction of pyridinium ions with potassium borohydride. He reported that 1-tetraacetylglucosidyl-3-carbamoylpyridinium bromide (28) was converted to the same dihydropyridine (29) by potassium borohydride or sodium dithionite. In light of current knowledge, the 1,4-dihydropyridine system must be assumed.

The structure of the dihydropyridines has been the subject of much research due to the presence of this structural feature in the reduced form of the coenzyme nicotinamide adenine dinucleotide. Usually, isomeric dihydropyridines are formed from the reductions of a pyridinium ion with sodium dithionite and with sodium borohydride. The sodium dithionite reduction product was shown to be structurally related to the reduced form of Coenzyme I, and the incorrect assignment as a 1,2-dihydropyridine by Karrer²³ confused the studies of the structure of the dihydropyridines from the sodium borohydride reduction of pyridinium ions. The chemical tests for distinguishing among the 1,4-, 1,2-, and 1,6-dihydropyridines proved to be unreliable, whereas ultraviolet absorption spectroscopy was shown to be successful for this purpose.^{5, 6, 8-10, 24-30} The 3-substituted-1,4- and -1,6-dihydropyridines have similar long wavelength absorption maxima, but the latter system also has an absorption band between 260 and 280 m μ . The 1,2-dihydropyridines having the same substituents as the 1,4- or 1,6-dihydropyridines have the long wavelength absorption band approximately 60-80 m μ bathochromically shifted from that of the 1,4- or 1,6-dihydropyridines (see Table II). A theoretical discussion of the spectra of 1,4- and 1,6-dihydronicotinamides has been presented by Cilento.³¹

²¹ J. J. Panouse, *Compt. Rend.* **233**, 260 and 1200 (1951).

²² J. J. Panouse, *Bull. Soc. Chim. France* 53D and 60D (1953).

²³ H. Kuhn, W. Traber, and P. Karrer, *Helv. Chim. Acta* **40**, 751 (1957).

²⁴ G. Stein and G. Stiasny, *Nature* **176**, 734 (1955).

²⁵ R. Segal and G. Stein, *J. Chem. Soc.* **1960**, 5254.

^{25a} Y. Paiss and G. Stein, *J. Chem. Soc.* **1958**, 2905.

²⁶ K. Wallenfels and H. Schüly, *Ann.* **621**, 86 and 106 (1959).

²⁷ K. Wallenfels and H. Schüly, *Angew. Chem.* **67**, 517 (1955).

²⁸ K. Wallenfels and H. Schüly, *Angew. Chem.* **69**, 505 (1957).

²⁹ K. Wallenfels and M. Gellrich, *Ann.* **621**, 149 and 178 (1959).

³⁰ K. Wallenfels and M. Gellrich, *Ber.* **92**, 1406 (1959).

³¹ G. Cilento, E. DeCarvalho Filho, and A. C. Giora Albanese, *J. Am. Chem. Soc.* **80**, 4472 (1958).

TABLE II
ULTRAVIOLET ABSORPTION SPECTRA OF DIHYDROPYRIDINES

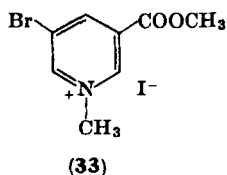
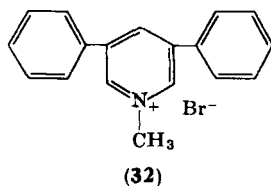
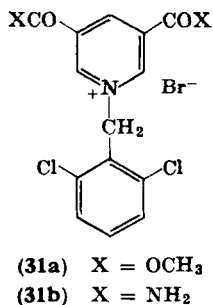
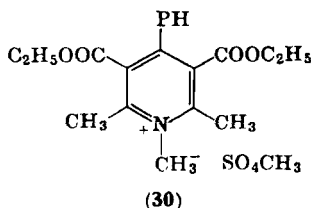
| 3-Substi- tuent | 1,4- | | 1,2- | | 1,6- | |
|--------------------|-----------------------------------|--------------------|---------------------------------|--------------------|-----------------------------|--------------------|
| | λ_{\max} (m μ) | Log ϵ | λ_{\max} (m μ) | Log ϵ | λ_{\max} (m μ) | Log ϵ |
| CN | 340 | 3.757 | 406 (H ₂ O– EtOH) | 3.60 ¹⁰ | 240 (EtOH) | 3.85 ¹⁰ |
| | 342.5 (H ₂ O– EtOH) | 3.86 ¹⁰ | | | 349 | 3.68 |
| COOCH ₃ | 363 (H ₂ O) | 3.86 ⁸ | 432 (H ₂ O) | 3.76 ¹⁰ | 263 (H ₂ O) | 3.76 ⁸ |
| | | | | | 362 | 3.84 |
| CONH ₂ | 350 (MeOH) | 3.88 ⁶ | 410 (MeOH) | 3.60 ⁵ | 265 | 3.99 ⁶ |
| | | | | | 355 (MeOH) | 3.87 |
| COPh | 385 (MeOH) | 3.86 ⁵ | 470 (MeOH) | 3.78 ⁵ | 300 (MeOH) | 3.48 ⁵ |
| | | | | | 369 | 3.85 |

On the basis of the foregoing generalizations, the reduction of pyridinium ions containing substituents at the 3- and 5-positions would be expected to give dihydropyridines as products. Such observations have been made by Traber and Karrer³² with 4-phenyl-1,2,6-trimethyl-3,5-diethoxycarbonylpyridinium methosulfate (30); by Wallenfels and Schöly²⁶ with 1-(2,6-dichlorobenzyl)-3,5-dimethoxycarbonyl (31a) and 3,5-diaminocarbonyl pyridinium bromides (31b); and by Anderson¹⁶ with 1-methyl-3,5-diphenylpyridinium bromide (32) and 1-methyl-3-bromo-5-methoxycarbonylpyridinium iodide (33). In each instance the major or only product was reported to be the 1,2-dihydro-derivative; however, the presence of 1,4-dihydropyridine isomers was demonstrated by NMR analysis of the latter two compounds. The last compound, the only example which is unsymmetrically substituted, underwent attack primarily at the position adjacent to the halogen, for only small yields of 1,4- and 1,6-isomers were detected. This is unexpected in view of the observations by several investigators that the sodium borohydride reduction of salts of unsubstituted nicotinic acid esters occurs with initial attack equally divided between the 2- and 6-positions.^{5,8-10}

A decrease in the ease of protonation of the intermediate dihydropyridine by addition of base has facilitated the isolation of these intermediates. Stein and co-workers^{24,25,25a} reported that the pH

³² W. Traber and P. Karrer, *Helv. Chim. Acta* **41**, 2066 (1958).

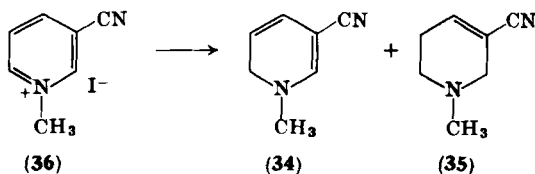
also affected the ratio of the dihydropyridines formed, for the reduction of 1-propyl-3-aminocarbonylpyridinium iodide at pH 11 gave predominantly 1-propyl-1,4-dihydronicotinamide, whereas with 1M sodium carbonate as solvent the reaction led to the 1,6-dihydro-isomer. Traber and Karrer³² found that 1-methyl-3-aminocarbonylpyridinium iodide was similarly affected by the pH of the reduction



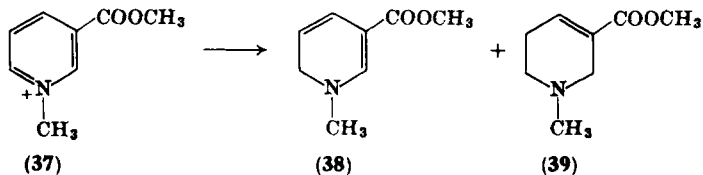
medium. In sodium bicarbonate the reaction gave a mixture of 1,4- and 1,6-dihydronicotinamides, whereas in 1N sodium hydroxide the 1,6-dihydronicotinamide was the major product contaminated with a small amount of the 1,2-dihydro-isomer. In the more strongly basic medium reduction of the 1,2-dihydropyridine to the tetrahydropyridine is retarded and leads to the isolation of this isomer. Thus Kinoshita and co-workers⁸⁻¹⁰ reported the isolation of approximately equal amounts of the 1,2- and 1,6-dihydro derivatives on reduction of 1-methyl-3-methoxycarbonylpyridinium bromide with sodium borohydride in 0.8 N sodium hydroxide in methanol. This procedure was used by Buchi and co-workers^{32a} as the key step in the synthesis of ibogamine.

^{32a} G. Buchi, D. L. Cotten, K. Kocsis, P. E. Sonnet, and F. E. Ziegler, *J. Am. Chem. Soc.* **87**, 2073 (1965).

The dihydropyridine formed by the initial attack of the borohydride ion will be stable to further reduction and be isolable under certain circumstances as indicated by the generalizations enumerated in Section I. The 1,4- and 1,6-dihydropyridines having an electron-withdrawing group in the 3-position also have been shown to be resistant to further reduction. The 1,4-dihydropyridine is seldom found as a major product; however, the 1,6-dihydropyridine often accompanies the tetrahydropyridine as a significant product.



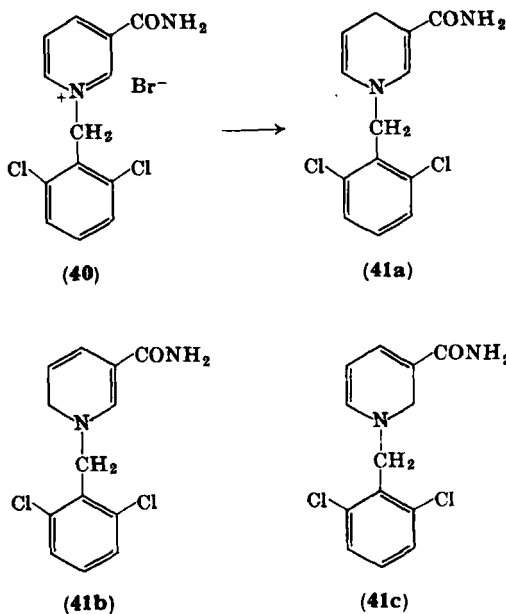
Schenker and Druey⁷ reported the isolation of 1-methyl-3-cyano-1,6-dihydropyridine (34) in equal amount (40–45%) with 1-methyl-3-cyano-1,2,5,6-tetrahydropyridine (35) from the reduction of 1-methyl-3-cyanopyridinium iodide (36). Similarly, Kinoshita⁸ reported the isolation of 28% of 1-methyl-3-methoxycarbonyl-1,6-dihydropyridine (38) and 34% of arecoline (39) from the reduction of 1-methyl-3-methoxycarbonylpyridinium iodide (37). Wallenfels and Schüly^{6, 26} found that the large 2,6-dichlorobenzyl-substituent on the nitrogen



caused the formation of some 1,4-dihydropyridine isomer (41a) from the reduction of 1-(2,6-dichlorobenzyl)-3-aminocarbonylpyridinium bromide (40) with sodium borohydride. The major product was the 1,6-dihydro-isomer (41b), and the presence of some 1,2-dihydro-isomer (41c) was detected by ultraviolet absorption spectroscopy.

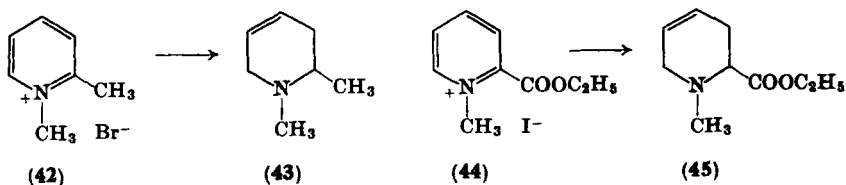
As mentioned previously, the 1-phenyl-1,2- and -1,4-dihydropyridines (22a and b) were resistant to further reduction because of the orbital overlap of the nitrogen lone-pair of electrons with those

of the phenyl substituent. Thus the steric or electronic interference to proton attack by a substituent attached to the enamine system of the dihydropyridine has resulted in the isolation of dihydropyridines from the reductions with sodium borohydride.



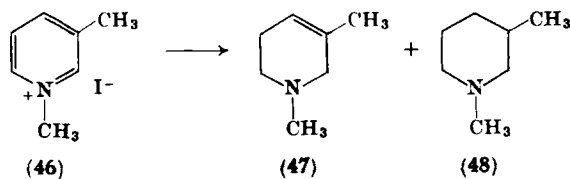
2. Formation of Tetrahydropyridines

The formation of tetrahydropyridines by the sodium borohydride reduction of a number of pyridinium ions has been mentioned in connection with the discussion of the intermediate dihydropyridines. The generalizations describing the reduction process would predict that the tetrahydro-product of the reduction of a 2-, 3-, or 4-mono-substituted pyridinium ion would be the 1,2,3,6- for the 2- and 4-substituted and the 1,2,5,6-tetrahydropyridines for the 3-substituted



pyridines. This is illustrated in the 2-series by the reduction of 1,2-dimethylpyridinium bromide (42) to 1,2-dimethyl-1,2,3,6-tetrahydropyridine (43),¹⁷ and 1-methyl-2-ethoxycarbonylpyridinium iodide (44) to ethyl 1-methyl-1,2,3,6-tetrahydropyridine-2-carboxylate (45).^{33, 33a}

The examples of reductions of 1,3-disubstituted pyridinium ions are numerous. If the 3-substituent is electron-withdrawing, the 1,2,5,6-tetrahydropyridine is the only tetrahydro-derivative isolated; however, the 1,6-dihydropyridine is often obtained as a second product (*vide supra*). Schenker³⁴ reported that both 1,2,3,6- and 1,2,5,6-tetrahydropyridines are formed from 1,3-disubstituted pyridinium ions depending upon the nature of the substituent; however, this observation has not been made by others. Kinoshita and Kawasaki¹⁰ indicated the possibility of the formation of both isomers from the reduction of 1,3-dimethylpyridinium iodide (46); however, they gave no evidence to indicate the nature of their product. This reaction was reported by others^{16,17} to lead to a mixture of 1,3-dimethyl-1,2,5,6-tetrahydropyridine (47) and 1,3-dimethylpiperidine (48). Other 1,3-disubstituted pyridinium ions in which the 3-substituent is not electron-withdrawing have also been reported to form exclusively the 1,2,5,6-tetrahydropyridine.^{35,36}



The 1,4-disubstituted pyridinium salts give excellent yields of the 1,2,3,6-tetrahydropyridines,^{11,16,34,37-39} for, as can be seen from the

³³ M. Ferles, *Collection Czech. Chem. Commun.* **24**, 3326 (1959); *Chem. Abstr.* **54**, 4575 (1960).

^{33a} See also H. Bruderer, M. Baumann, M. Uskokovic, and A. Brossi, *Helv. Chim. Acta*, **47**, 1852 (1964).

³⁴ K. Schenker, *Angew. Chem.* **72**, 638 (1960).

³⁵ J. W. Huffman, *J. Org. Chem.* **27**, 503 (1962).

³⁶ E. Wenkert, R. A. Massy-Westropp, and R. G. Lewis, *J. Am. Chem. Soc.* **84**, 3732 (1962).

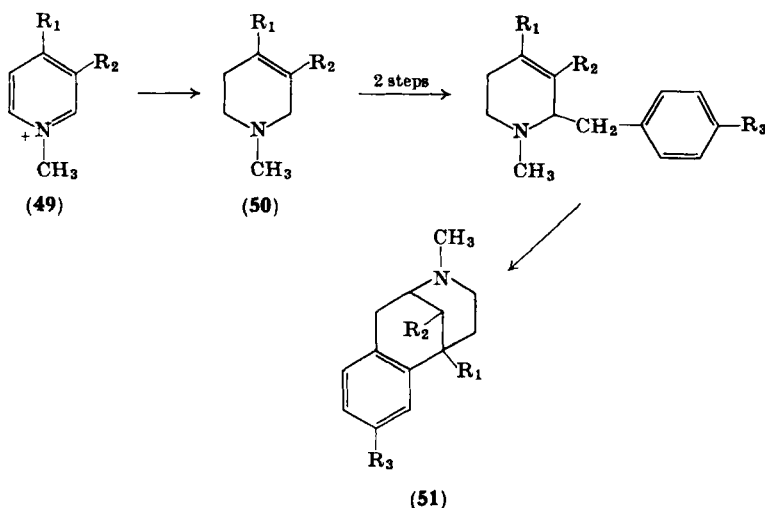
³⁷ E. W. Warnhoff, *J. Org. Chem.* **27**, 4587 (1962).

³⁸ S. Saito and E. L. May, *J. Org. Chem.* **27**, 948 (1962).

³⁹ R. C. Elderfield, B. A. Fischer, and J. M. Lagowski, *J. Org. Chem.* **22**, 1376 (1957).

generalizations described above, initial attack of the borohydride would be directed to the 2- (6-) position, giving no isomeric intermediates. Protonation and subsequent borohydride reduction of the tetrahydropyridine could occur without interference by the substituent.

The reduction of tri- and polysubstituted pyridinium ions has not received extensive attention, and generalizations are not available. A 1,2,4-trisubstituted pyridinium ion has been shown to form a 1,2,3,6-tetrahydropyridine,¹⁵ and 1,3,4-trisubstituted pyridinium salts (49) are reported to give 1,2,5,6-tetrahydropyridines (50) which were useful as intermediates in the synthesis of benzomorphans (51).⁴⁰⁻⁴³ As discussed above, those pyridinium ions having substituents on both the 3- and 5-positions usually lead to stable dihydropyridines on reduction with sodium borohydride.^{43a}



This procedure for the partial reduction of the pyridine ring has been applied to the synthesis of arecoline,^{8, 21, 44, 45} 1-substituted-3-

⁴⁰ E. M. Fry and E. L. May, *J. Org. Chem.* **26**, 2592 (1961).

⁴¹ J. H. Ager and E. L. May, *J. Org. Chem.* **27**, 245 (1962).

⁴² S. E. Fullerton, J. H. Ager, and E. L. May, *J. Org. Chem.* **27**, 2554 (1962).

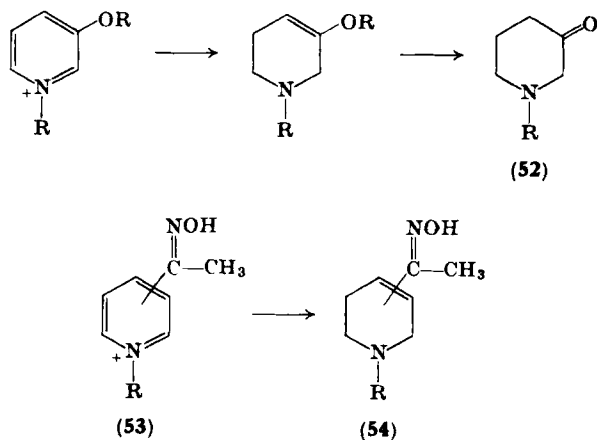
⁴³ J. H. Ager, S. E. Fullerton, and E. L. May, *J. Med. Chem.* **6**, 322 (1963).

^{43a} E. M. Fry, *J. Org. Chem.* **28**, 1869 (1963).

⁴⁴ T. Tsukamoto, N. Kinoshita, and A. Ando, *Yakugaku Zasshi* **82**, 1317 (1962); *Chem. Abstr.* **59**, 558 (1963).

⁴⁵ R. E. Lyle, E. Perlowski, H. Troscianiec, and G. G. Lyle, *J. Org. Chem.* **20**, 1761 (1955).

and 4-piperidones (**52**),⁴⁶ and intermediates in the synthesis of benzomorphans (*vide supra*).³⁹⁻⁴³ In view of the difficulty in effecting the catalytic hydrogenation of pyridinium iodides, Huffman³⁵ utilized the sodium borohydride reduction followed by catalytic hydrogenation as a more convenient method of forming the piperidine ring than exchanging the anion of the pyridinium salt followed by catalytic hydrogenation. The oximino function being unaffected by sodium borohydride allowed the preparation of α,β -unsaturated-ketoximes (**54**) by the sodium borohydride reduction of quaternary salts of pyridyl methyl ketoximes (**53**).⁴⁷



The quaternary salts of ketals of 4-pyridyl alkyl and aryl ketones undergo reduction with sodium borohydride to give the expected 1,2,3,6-tetrahydropyridines.^{47a} Reduction of an analogous ketal of a quaternary salt of a 3-pyridyl ketone led to rupture of the ketal ring.^{47b}

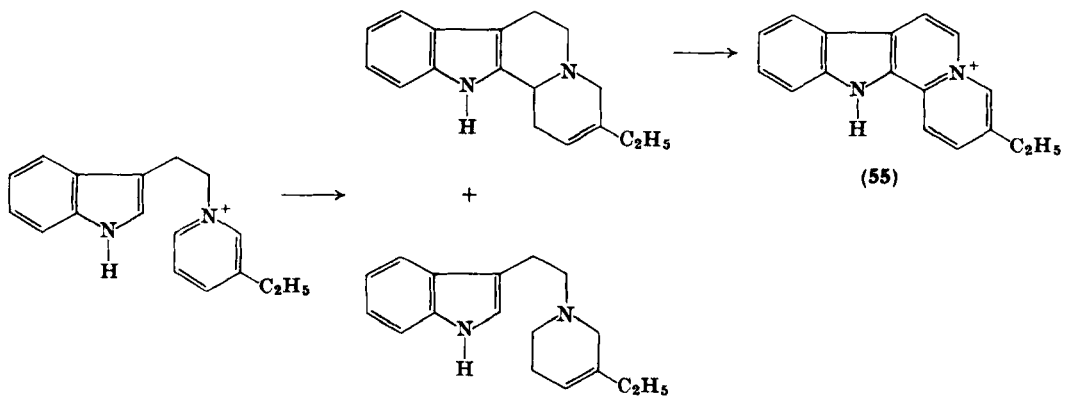
The intermediate dihydropyridines from the sodium borohydride reduction have been converted to tetrahydropyridines via cyclizations involving nucleophilic aromatic rings. The cyclization step is exactly analogous to the second attack of the borohydride ion on the protonated dihydropyridine. This synthetic pathway was used by

⁴⁶ R. E. Lyle, R. E. Adel, and G. G. Lyle, *J. Org. Chem.* **24**, 342 (1959).

⁴⁷ J. Druey and K. Schenker, U.S. Patent 3,004,979 (1960); *Chem. Abstr.* **56**, 3463 (1962).

^{47a} R. Hill, Senior Thesis, University of New Hampshire, Durham, 1965.

^{47b} F. Bohlmann, D. Schumann, and H. Schulz, *Tetrahedron Letters*, No. 3, 171 (1965).



Wenkert *et al.*³⁶ to prepare flavopereirine alkaloids (55), although the method was not as successful as that using lithium aluminum hydride (*vide infra*).

The reduction of a pyridinium ion in the presence of hydrogen cyanide has been shown to produce substituted 6-cyano-1,2,5,6-tetrahydropyridines. The cyanide competes with the borohydride ion for reaction with the protonated dihydropyridine intermediate. The cyanide addition can be reversed, and this reaction, therefore, provides a method of protecting the intermediate dihydropyridine from reduction by sodium borohydride.^{47a}

Reviews of the reduction of pyridinium ions by alkali metal hydrides have provided partial surveys of this subject to the time of their publication.^{22, 48-51, 51a}

B. REDUCTION OF PYRIDINES AND PYRIDINIUM SALTS WITH LITHIUM ALUMINUM HYDRIDE

The important application of lithium aluminum hydride (LAH) for the reduction of functional groups containing multiple oxygen bonds led to the early discovery that the reduction of such functional groups on the pyridine ring often occurred in poor yields. In particular this was noted in the vitamin B syntheses.^{52, 52a} Hochstein⁵³ observed in 1949 that pyridine rings were attacked by lithium aluminum hydride; however, reduction of pyridine carboxylic acid derivatives to pyridine methanols has been reported by Jones and Kornfeld,⁵⁴ Micovic and Mihailovic,⁵⁵ Bigot^{52a} and Cohen and his co-workers.⁵² These authors observed attack of the pyridine ring only as a side reaction or not at all. In each case, however, precautions were observed to ensure that the

^{47a} E. M. Fry, *J. Org. Chem.* **29**, 1647 (1964).

⁴⁸ R. M. Acheson, "An Introduction to the Chemistry of Heterocyclic Compounds," pp. 170-171. Wiley (Interscience), New York, 1960.

⁴⁹ R. A. Barnes, in "Pyridine and Its Derivatives" (E. Klingsberg, ed.), Part 1, pp. 77-79. Wiley (Interscience), New York, 1960.

⁵⁰ E. N. Shaw, in "Pyridine and Its Derivatives" (E. Klingsberg, ed.), Part 2, pp. 47-55. Wiley (Interscience), New York, 1961.

⁵¹ E. Schenker, *Angew. Chem.* **73**, 81 (1961).

^{51a} See also R. F. Evans, *Rev. Pure Appl. Chem.* **15**, 23 (1965).

⁵² A. Cohen, J. W. Haworth, and E. G. Hughes, *J. Chem. Soc.* **1952**, 4374.

^{52a} J. A. Bigot, Thesis, University of Amsterdam, Netherlands, 1957.

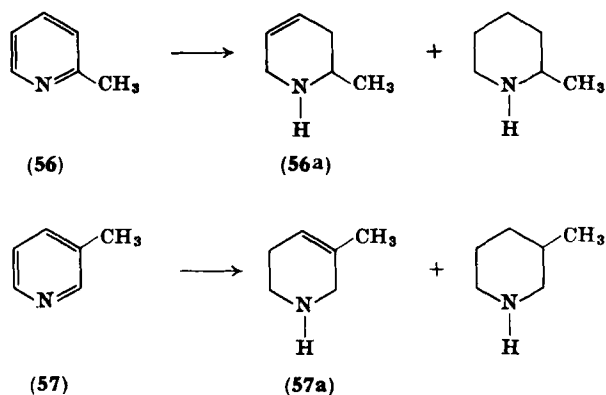
⁵³ F. A. Hochstein, *J. Am. Chem. Soc.* **71**, 305 (1949).

⁵⁴ R. G. Jones and E. C. Kornfeld, *J. Am. Chem. Soc.* **73**, 107 (1951).

⁵⁵ V. M. Micovic and M. L. Mihailovic, *Rec. Trav. Chim.* **71**, 970 (1952).

pyridine would be in the presence of excess LAH for only a short time. The preparation of pyridinyl methanols by reduction has been reviewed.^{51, 52a, 56}

Derivatives of pyridine-3,5-dicarboxylic acid have been shown to undergo reaction with lithium aluminum hydride by attack on the pyridine ring to form 1,4-dihydropyridines.^{57, 58} Presumably the decrease in electron-density at the ring carbon atoms due to these substituents causes the ring to be extremely susceptible to hydride attack. Similar results were obtained with 3,5-dicyanopyridine derivatives. Methyl nicotinate, however, underwent reaction with LAH with exclusive reduction of the ester function.⁵⁷ Recently the 3,5-dicyanopyridines have been reported to give mixtures of 1,2- and 1,4-dihydropyridines on reduction with LAH or sodium borohydride.^{20a}



Ferles reported that tetrahydropyridines and piperidines were formed by the reaction of pyridines with lithium aluminum hydride and aluminum chloride in ether.⁵⁹ 2-Methyl-1,2,3,6-tetrahydropyridine (56a) was formed by the reduction of α -picoline (56), whereas 3-methyl-1,2,5,6-tetrahydropyridine (57a) was produced by the

⁵⁶ E. V. Brown, in "Pyridine and Its Derivatives" (E. Klingsberg, ed.), Part 4, pp. 1-122. Wiley (Interscience), New York, 1964.

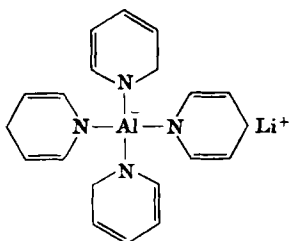
⁵⁷ F. Bohlmann and M. Bohlmann, *Ber.* **86**, 1419 (1953).

⁵⁸ F. Bohlmann, A. Englisch, J. Politt, H. Sander, and W. Weise, *Ber.* **88**, 1831 (1955).

⁵⁹ M. Ferles, *Sb. Vysoke Skoly Chem.-Technol. Praze Oddil Fak. Anorg. Org. Technol.* **1960**, 519-523; *Chem. Abstr.* **55**, 24740 (1961).

reduction of β -picolone (57). The similarity of these products with those formed by the reduction of the corresponding pyridinium ion with sodium borohydride suggests that the mechanisms of these reductions are probably related, differing only in the Lewis acid which attacks the intermediate dihydropyridine.

A very extensive investigation of the reaction of pyridine and lithium aluminum hydride has been made by Lansbury and Peterson.⁶⁰⁻⁶² These authors found that an aged solution of LAH in pyridine possessed unusual and selective reductive properties. Ketones and aldehydes were reduced while carboxylic acids were not, and diaryl ketones were reduced more readily than dialkyl ketones. These distinctive properties were found to result from a dihydropyridine-aluminum complex formed by the reaction of LAH and pyridine.



The reduction of pyridinium quaternary salts with LAH has been reported to yield dihydro- and tetrahydropyridines, depending upon the structure of the salt and the conditions of the reaction. Kuss and Karrer⁶³ reported the formation of a 1,2-dihydropyridine from the reaction of 1,2,6-trimethyl-4-phenyl-3,5-diethoxycarbonylpyridinium methosulfate and lithium aluminum hydride in ether. Ferles⁶⁴ indicated that 1,3-dimethylpyridinium iodide (46) gave exclusively 1,3-dimethyl-1,2,5,6-tetrahydropyridine (47) on reaction with LAH in chloroform.

The reduction of 1-(β -3-indolyethyl)pyridinium ions (58) with lithium aluminum hydride was investigated as a means of causing cyclization to indolo-quinolizines (58a). These reactions gave as the

⁶⁰ P. T. Lansbury and J. O. Peterson, *J. Am. Chem. Soc.* **83**, 3537 (1961).

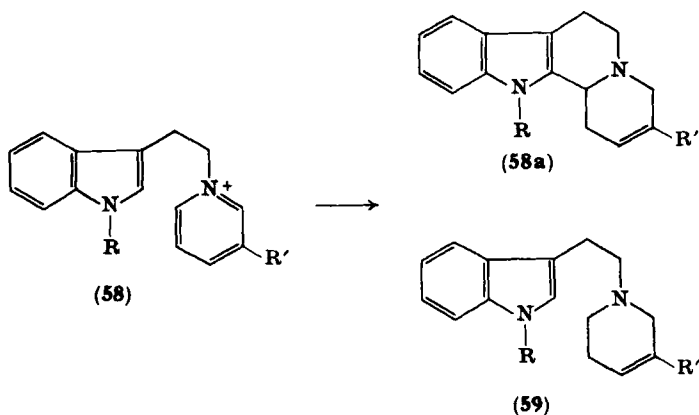
⁶¹ P. T. Lansbury and J. O. Peterson, *J. Am. Chem. Soc.* **84**, 1756 (1962).

⁶² P. T. Lansbury and J. O. Peterson, *J. Am. Chem. Soc.* **85**, 2236 (1963).

⁶³ L. Kuss and P. Karrer, *Helv. Chim. Acta* **40**, 740 (1957).

⁶⁴ M. Ferles, *Chem. Listy* **52**, 674 (1958); *Chem. Abstr.* **52**, 13724 (1958).

major product the corresponding 1,2,3,6-tetrahydropyridine (59)³⁹ with small amounts of the indolo-quinolizine (58a).³⁶ This anomalous reduction of the pyridinium ion to the tetrahydropyridine in a non-reactive solvent has been proposed as resulting from an intramolecular reduction of the intermediate 1,2-dihydropyridine by an aluminohydride complex bonded to the indole nitrogen. Support for this hypothesis was obtained by a study of the reduction of the analog having a methyl substituent on the indole nitrogen. This reaction gave as the only product the indolo-quinolizine (58a). Similarly, the use of lithium tri-*t*-butoxyaluminum hydride for reduction of the 1-(β -3-indolyethyl)pyridinium salts (58) gave largely indolo-quinolizines (58a).³⁶ The course of these cyclizations is considered in more detail in Section III,B.

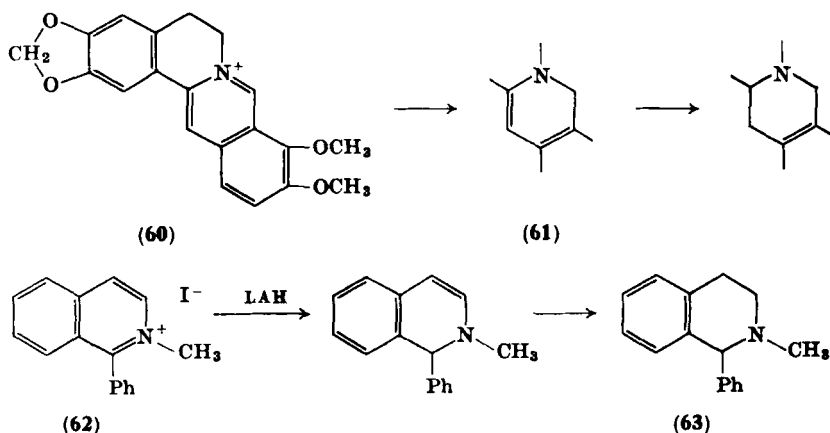


III. Complex Metal Hydride Reduction of Isoquinolines and Isoquinolinium Ions

The reduction of isoquinolinium ions has been extensively investigated with borohydride and aluminum hydride ions. The use of borohydride ion in a protonic solvent normally leads to the formation of 1,2,3,4-tetrahydroisoquinolines, whereas the reduction with aluminum hydride ion in an aprotic medium generally gives a 1,2-dihydroisoquinoline. This 1,2-dihydroisoquinoline contains an enamine system and may undergo further reaction on treatment with acid. The 1,2- and 3,4-dihydroisoquinolines as well as isoquinolinium ions are reduced by the borohydride ion in a protonic medium to the 1,2,3,4-tetrahydroisoquinolines.

A. REDUCTION OF ISOQUINOLINIUM IONS AND DIHYDRO-ISOQUINOLINES WITH BOROHYDRIDE

The reduction of 2-substituted-isoquinolinium salts has been reported by Torossian⁶⁵ with potassium borohydride in water, by Mirza,⁶⁶ and by Durmand *et al.*,^{67,68} using sodium borohydride in aqueous methanol to yield 1,2,3,4-tetrahydroisoquinolines. The reduction of the second double bond appears to arise from a mechanism similar to that leading to tetrahydropyridines from pyridinium ions (see Section I). Mirza⁶⁶ (see also Bose⁶⁹) found that the reduction of berberine (60) with sodium borohydride could be stopped at the 1,2-dihydro-intermediate (61), and Karrer and Brook⁷⁰ showed that the 1,2-dihydroisoquinoline formed by the lithium aluminum hydride reduction of 1-phenyl-2-methylisoquinolinium iodide (62) could be further reduced to the 1,2,3,4-tetrahydroisoquinoline (63) with sodium borohydride in methanol. Awe *et al.*^{71,72} and Huffman⁷³



⁶⁵ R. Torossian, *Compt. Rend.* **235**, 1312 (1952).

⁶⁶ R. Mirza, *J. Chem. Soc.* **1957**, 4400.

⁶⁷ X. Lusinch, S. Durmand, and R. Delaby, *Compt. Rend.* **248**, 426 (1959).

⁶⁸ S. Durmand, X. Lusinch, and R. C. Moreau, *Bull. Soc. Chim. France* **1961**, 270.

⁶⁹ S. Bose, *J. Indian Chem. Soc.* **32**, 450 (1955); *Chem. Abstr.* **50**, 10748 (1956).

⁷⁰ P. R. Brook and P. Karrer, *Helv. Chim. Acta* **40**, 260 (1957).

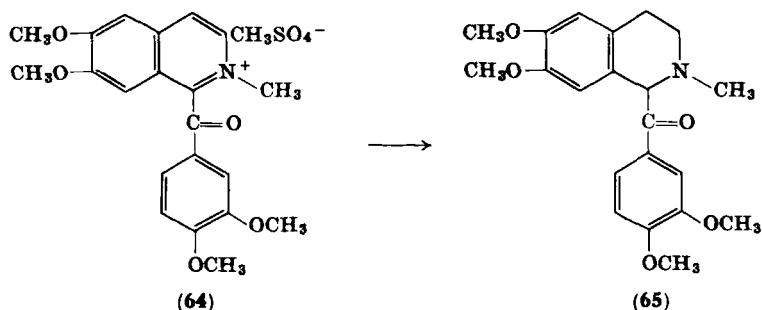
⁷¹ W. Awe, H. Wichmann, and R. Buerhop, *Ber.* **90**, 1997 (1957).

⁷² W. Awe and R. Buerhop, *Arch. Pharm.* **294**, 178 (1961); *Chem. Abstr.* **55**, 15531 (1961).

⁷³ J. W. Huffman, *J. Am. Chem. Soc.* **80**, 5193 (1958).

demonstrated similar conversions of 1,2-dihydroisoquinolines to the corresponding 1,2,3,4-tetrahydroisoquinolines by reduction with sodium borohydride in protonic medium.

The reduction of the isoquinolinium ring was shown to occur more rapidly than that of the carbonyl group of a 1-aryl substituent. Thus the reduction of 1-(3,4-dimethoxybenzoyl)-6,7-dimethoxy-2-methyl-isoquinolinium methosulfate (**64**) in aqueous sodium carbonate gave 1-(3,4-dimethoxybenzoyl)-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**65**). In alcohol, both the ring and carbonyl groups underwent reduction.⁷⁴



A number of partially reduced isoquinolines and isoquinolines having fused rings (**66**–**69**) have been reduced by sodium borohydride with the results indicated opposite^{75–77}:

B. REDUCTION OF ISOQUINOLINIUM SALTS WITH LITHIUM ALUMINUM HYDRIDE

The reduction of isoquinolinium salts to 1,2-dihydroisoquinolines was first reported by Schmid and Karrer^{78,79} and has been exploited many times.^{80–82} The novel and practical application of this inter-

⁷⁴ K. W. Bentley and A. W. Murray, *J. Chem. Soc.* **1963**, 2487.

⁷⁵ B. Witkop, *J. Am. Chem. Soc.* **75**, 3361 (1953).

⁷⁶ G. B. Marini-Bettolo and J. Schmutz, *Helv. Chim. Acta* **42**, 2146 (1959).

⁷⁷ W. Schneider and B. Müller, *Ber.* **93**, 1579 (1960).

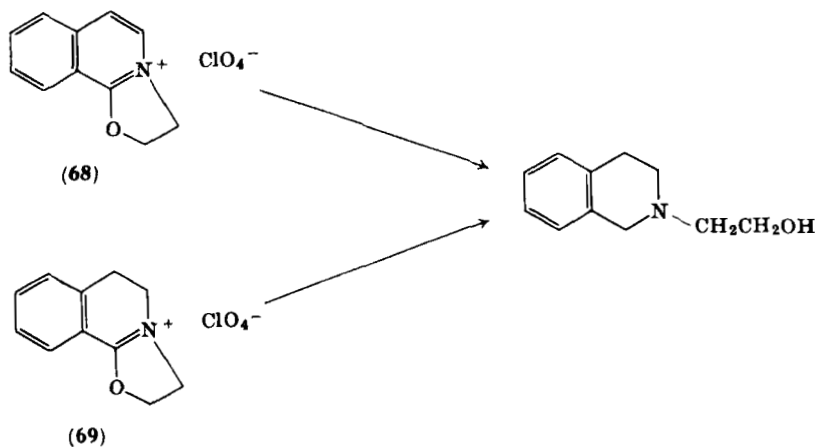
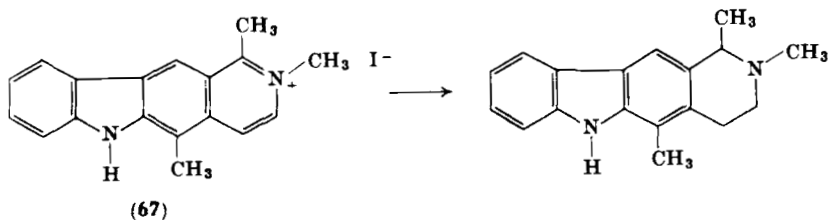
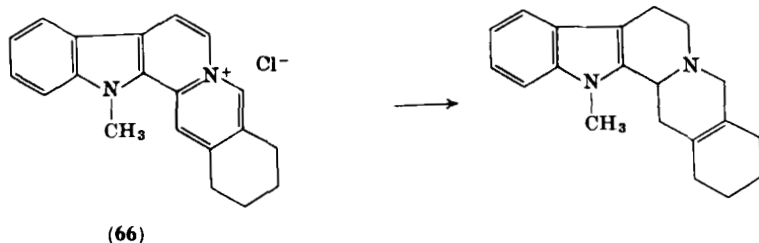
⁷⁸ H. Schmid and P. Karrer, *Helv. Chim. Acta* **32**, 960 (1949).

⁷⁹ P. Karrer, *Bull. Soc. Chim. France* **1950**, 907.

⁸⁰ A. R. Battersby, D. J. LeCount, J. Garratt, and R. I. Thrift, *Tetrahedron* **14**, 46 (1961).

⁸¹ S. F. Dyke and M. Sainsbury, *Tetrahedron Letters* No. 24, 1545 (1964).

⁸² R. C. Elderfield, J. M. Lagowski, O. L. McCurdy and S. L. Wythe, *J. Org. Chem.* **23**, 435 (1958).

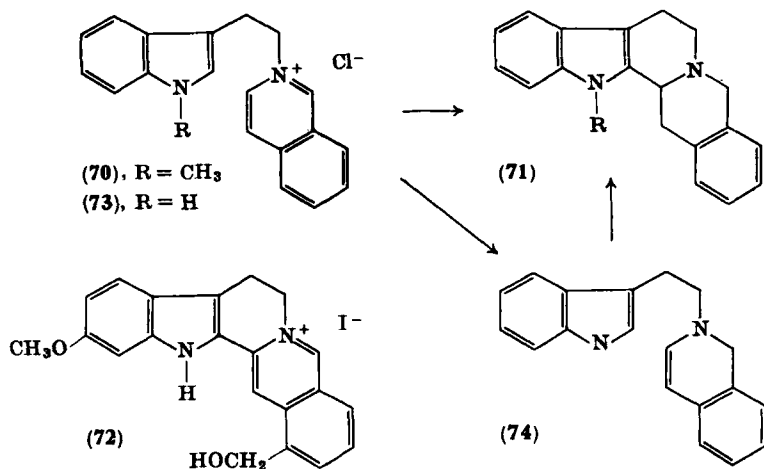


mediate to the synthesis of quinolizine derivatives will serve to illustrate the reaction. Belleau⁸³ and Potts and Robinson⁸⁴ showed that the reduction of 2- β -(3-indolyethyl)-isoquinolinium chloride (70) with lithium aluminum hydride gave 5,6,7,8,13a,13b-hexahydro-benz[*g*]indolo-[2,3-*a*]quinolizine (71). Belleau⁸³ also provided evidence

⁸³ B. Belleau, *Chem. Ind. (London)* **1955**, 229.

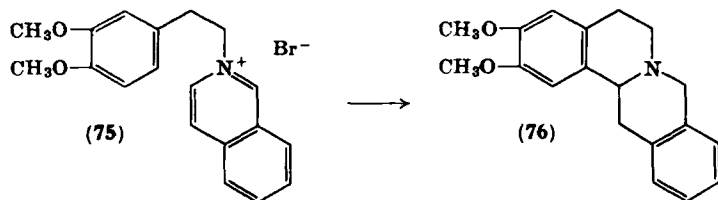
⁸⁴ K. T. Potts and R. Robinson, *J. Chem. Soc.* **1955**, 2675.

for the related cyclization observed by Julian and Printy.⁸⁵ The reaction was used by Elderfield and Fischer^{86,87} for the synthesis of alstonilol iodide (72), and was investigated from a mechanistic standpoint by J. W. Huffman⁷³ who showed that the lithium aluminum



hydride converted the isoquinolinium salt (73) to the 1,2-dihydroisoquinoline (74). The enamine system of the dihydroisoquinoline was protonated during the work-up of the reaction, and the electrophilic, incipient-aldehyde carbon attacks the nucleophilic 2- or 3-position of the indole ring to give the new ring as indicated below. This same reaction sequence has been applied with other nitrogen heterocycles (see Section II, A, 2).

A similar route was used by Huffman⁸⁸ for the conversion of 2- $[\beta$ -(3,4-dimethoxyphenyl)ethyl]isoquinolinium bromide (75) to 2,3-dimethoxyberbine (76). The 1,2-dihydroisoquinoline was isolated as



⁸⁵ P. L. Julian and H. C. Printy, *J. Am. Chem. Soc.* **71**, 3206 (1949).

⁸⁶ R. C. Elderfield and B. A. Fischer, *J. Org. Chem.* **23**, 332 (1958).

⁸⁷ R. C. Elderfield and B. A. Fischer, *J. Org. Chem.* **23**, 949 (1958).

⁸⁸ J. W. Huffman and E. G. Miller, *J. Org. Chem.* **25**, 90 (1960).

an intermediate, again showing the pathway of the cyclization reaction. Variations of this cyclization reaction have been reported by Ribbens and Nauta⁸⁹ and Liljegren and Potts.⁹⁰

C. REDUCTION OF ISOQUINOLINE WITH LITHIUM ALUMINUM HYDRIDE OR DIALKYL ALUMINUM HYDRIDE

The isoquinoline ring undergoes attack by the nucleophilic aluminum hydride anion in much the same manner as the pyridine ring to produce 1,2-dihydroisoquinolines,^{91, 92} although tetrahydroisoquinolines have been reported as products even though no proton source was apparently present.⁹² (For a probable mechanism see Section IV, B.) The reduction of isoquinoline *N*-oxide by lithium aluminum hydride was also reported to yield the 1,2-dihydroisoquinoline.⁹³

The isoquinoline ring has been shown to be selectively reduced to the dihydro- or tetrahydroisoquinoline by diisobutylaluminum hydride, depending upon the ratio of reducing agent employed. The reaction has been employed to prepare 1,2-dihydroisoquinoline or 1,2,3,4-tetrahydroisoquinoline in high yields.⁹⁴

IV. Complex Metal Hydride Reduction of Quinolines and Quinolinium Salts

The reduction of quinolines, unlike that of isoquinolines, with complex metal hydrides can occur with attack of the hydride at the 2- or 4-position. As with the pyridines, the predominant attack appears to be at the 2-position to form 1,2-dihydroquinolines; the 1,4-dihydroquinolines and 1,2,3,4-tetrahydroquinolines formed by initial attack at the 4-position are the minor products. As a consequence, 1,2,3,4-tetrahydroquinolines are best prepared only by the sodium borohydride reduction of quinolinium salts.⁶⁵

A. REDUCTIONS WITH SODIUM BOROHYDRIDE

Quinolinium salts are converted by sodium borohydride to the corresponding 1,2,3,4-tetrahydroquinolines as the major product. Usually, however, small amounts of 1,2-dihydroquinoline can be

⁸⁹ C. Ribbens and W. T. Nauta, *Rec. Trav. Chim.* **79**, 854 (1960).

⁹⁰ D. R. Liljegren and K. T. Potts, *J. Org. Chem.* **27**, 377 (1962).

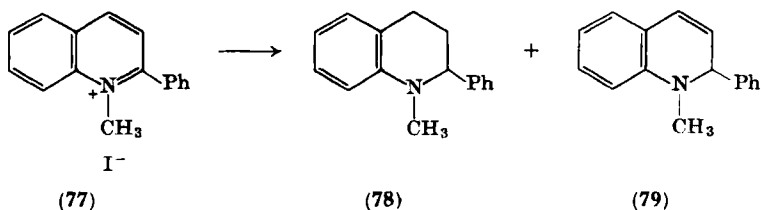
⁹¹ L. M. Jackman and D. I. Packham, *Chem. Ind. (London)* **1955**, 360.

⁹² E. A. Braude, J. Hannah, and R. P. Linstead, *J. Chem. Soc.* **1960**, 3249.

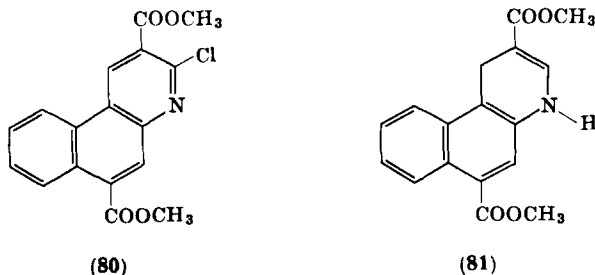
⁹³ W. Traber, P. Karrer, and M. Hubman, *Helv. Chim. Acta* **43**, 265 (1960).

⁹⁴ W. P. Neumann, *Ann.* **618**, 90 (1958).

detected in the crude reaction product. Thus 1-methyl-2-phenylquinolinium iodide (**77**) gave 84% of 1,2,3,4-tetrahydroquinoline (**78**) and 16% of 1,2-dihydroquinoline (**79**).⁹⁵



As would be expected, the weaker reducing agent, sodium borohydride, has received little attention for the reduction of quinolines. The reaction of 2-chloro-3,7-dicarbomethoxy-5,6-benzoquinoline (**80**) has been reported by Walker to yield 3,7-dicarbomethoxy-5,6-benzo-1,4-dihydroquinoline (**81**) on reaction with sodium borohydride.⁹⁶ The success of this reaction may depend upon the electron-withdrawing properties of the carbomethoxy groups.



B. REDUCTIONS WITH LITHIUM ALUMINUM HYDRIDE

The reduction of quinolinium salts or quinolines with lithium aluminum hydride gives predominantly the 1,2-dihydroquinolines.^{78, 92, 95, 97-103} The yield of product appears to depend upon the

⁹⁵ R. C. Elderfield and B. H. Wark, *J. Org. Chem.* **27**, 543 (1962).

⁹⁶ G. N. Walker and B. N. Weaver, *J. Org. Chem.* **26**, 4441 (1961).

⁹⁷ F. Bohlmann, *Ber.* **85**, 390 (1952).

⁹⁸ K. W. Rosenmund and F. Zymalkowski, *Ber.* **86**, 37 (1953).

⁹⁹ D. Craig and E. C. Gregg, *J. Am. Chem. Soc.* **75**, 2252 (1953).

¹⁰⁰ R. F. Collins, *J. Chem. Soc.* **1954**, 3641.

¹⁰¹ K. W. Rosenmund, F. Zymalkowski, and N. Schwarte, *Ber.* **87**, 1229 (1954).

¹⁰² K. Sutter-Kostic and P. Karrer, *Helv. Chim. Acta* **39**, 677 (1956).

¹⁰³ A. Richardson, Jr., and E. D. Amstutz, *J. Org. Chem.* **25**, 1138 (1960).

nature and position of substituents on the heterocyclic ring. This is interesting in view of the possibility of attack by the reagent at either the 2- or 4-positions. Braude *et al.*⁹² have presented evidence for the formation of a small yield of 1,4-dihydroquinoline on the reduction of quinoline under vigorous conditions, but even in this reaction the major product was 1,2-dihydroquinoline. Elderfield and Wark⁹⁵ reported that the reduction of 1-methyl-2-phenylquinolinium iodide gave a small yield of the 1,2,3,4-tetrahydroquinoline and proposed that the reduction occurred by initial attack of the hydride ion at the 4-position. The ratio of tetrahydro to dihydro varied with solvent and anion of the quinolinium salt. Since the reduction of 1,2-dimethylquinolinium iodide gave a small yield of the tetrahydroquinoline in addition to the major product, 1,2-dimethyl-1,2-dihydroquinoline, it is probable that the hydride attack with lithium aluminum hydride is subject to the same steric interference observed with the sodium borohydride reduction of pyridinium ions (see Section I).

V. Reduction of Non-aromatic Heterocycles Containing the C=N Function

The carbon–nitrogen double bond in cyclic Schiff's bases can be reduced by either borohydride or aluminum hydride ions. Examples in the literature are so numerous that only a few representative examples will be mentioned to indicate the scope of the reaction.

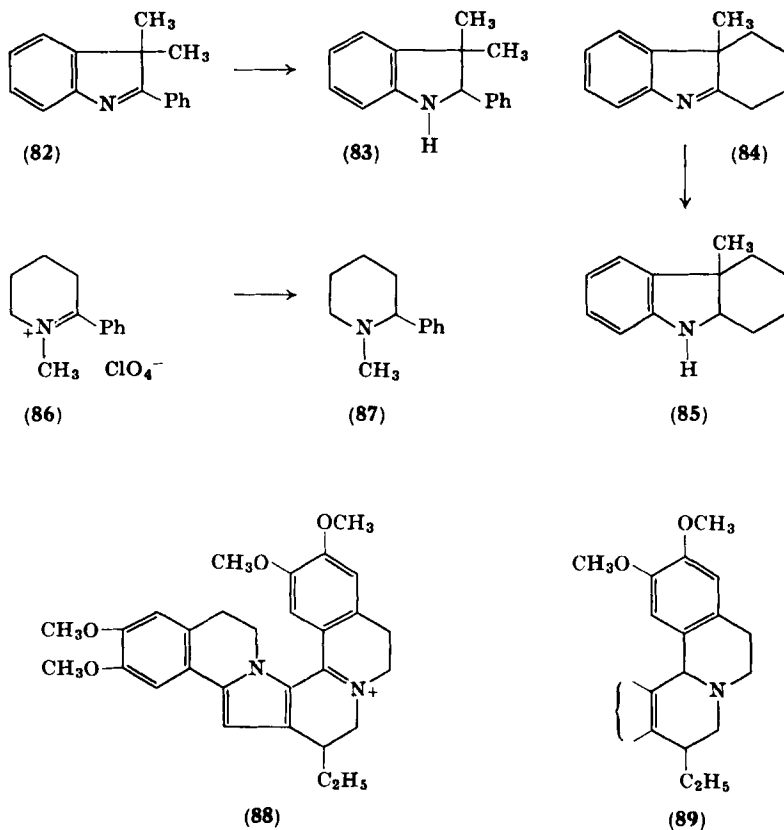
3-*H*-Indoles (indolenines) (**82**) are converted into indolines (**83**) by sodium borohydride,¹⁰⁴ and the related 4a-methyl-1,2,3,4-tetrahydro-4a-*H*-carbazole (**84**) was converted into the hexahydro-derivative (**85**) with lithium aluminum hydride.¹⁰⁵ Červinka¹⁰⁶ caused a partial asymmetric conversion of 1-methyl-2-phenyl-3,4,5,6-tetrahydropyridinium perchlorate (**86**) to 1-methyl-2-phenylpiperidine (**87**) by reduction with sodium borohydride in an ethereal solution of (–)-menthol. The carbon–nitrogen double bond of various derivatives of 3,4-dihydroisoquinolines has been reduced by sodium or potassium borohydride using the free bases,¹⁰⁷ the proton

¹⁰⁴ F. J. Evans, G. G. Lyle, J. Watkins, and R. E. Lyle, *J. Org. Chem.* **27**, 1553 (1962).

¹⁰⁵ P. Cerutti and H. Schmid, *Helv. Chim. Acta* **45**, 1992 (1962).

¹⁰⁶ O. Červinka, *Collection Czech. Chem. Commun.* **26**, 673 (1961); *Chem. Abstr.* **55**, 15479 (1961).

¹⁰⁷ S. Sugawara and M. Onda, Japanese Patent 1,779 (1961); *Chem. Abstr.* **56**, 8694 (1962).



salts,^{108, 109} and the quaternary salts.¹¹⁰⁻¹¹⁴ Partially reduced quino-
lizinium salts undergo reduction of the carbon-nitrogen double bond
with potassium borohydride,¹¹⁵ and the related rubremetinium

¹⁰⁸ J. Gardent, *Ann. Pharm. Franc.* **18**, 381 (1960); *Chem. Abstr.* **55**, 539 (1961).

¹⁰⁹ F. Hoffmann-LaRoche and Co., British Patent 862,052 (1961); *Chem. Abstr.* **55**, 19958 (1961).

¹¹⁰ M. Sasamoto, *Chem. Pharm. Bull. (Tokyo)* **8**, 324 (1960); *Chem. Abstr.* **55**, 10448 (1961).

¹¹¹ I. T. Strukov, *Zh. Obshch. Khim.* **31**, 2709 (1961); *Chem. Abstr.* **56**, 11567 (1962).

¹¹² J. Knabe and J. Kubitz, *Naturwissenschaften* **48**, 669 (1961).

¹¹³ M. F. Grundon, *J. Chem. Soc.* **1959**, 3010.

¹¹⁴ W. M. Whaley and C. N. Robinson, *J. Am. Chem. Soc.* **75**, 2008 (1953).

¹¹⁵ J. M. Osbond, *J. Chem. Soc.* **1961**, 4711.

bromide¹¹⁶ or chloride¹¹⁷ (88) was converted to the dihydro-derivative (89) with lithium aluminum hydride in ether.

The conversion of 5,6-dihydro-1,3-thiazines to 1,3-thiazines has been reported to occur on reduction with sodium borohydride in water at pH 5-7.^{117a} Similar success was reported with thiazoline,^{117b} although sodium borohydride in alcohol was reported to be ineffectual with highly substituted thiazolines.^{117c} Dibenzoxazepines are converted to dihydro derivatives by means of the action of sodium borohydride on the carbon—nitrogen double bond.^{117d} Quinolizinium ion undergoes ring cleavage on reaction with the Grignard reagent, sodium borohydride, or lithium aluminum hydride.^{117e}

VI. Reductions of Other Heterocycles Containing One Nitrogen Atom

A. PHENANTHRIDINE

The reduction of phenanthridine to 5,6-dihydrophenanthridine (90, R = H) was readily accomplished by reaction with lithium aluminum hydride in ethereal solution.¹¹⁸ The same dihydrophenanthridine resulted from the lithium aluminum hydride reduction of 6-chlorophenanthridine or phenanthridone,^{118a} thus confirming the position of saturation of the product.¹¹⁹ It is of interest to note that molecular complexes of phenanthridine and dihydrophenanthridine were not observed as products in this reduction as was the case in the metal hydride reduction of phenazine.¹¹⁹

Phenanthridine methiodide underwent a facile reduction to *N*-methyl-5,6-dihydrophenanthridine (90, R = CH₃) with lithium aluminum hydride in ethereal solution.¹²⁰ It was found that the use of

¹¹⁶ P. Karrer and O. Rüttner, *Helv. Chim. Acta* **33**, 291 (1950).

¹¹⁷ R. F. Tietz and W. E. McEwen, *J. Am. Chem. Soc.* **75**, 4945 (1953).

^{117a} J. C. Getson, J. M. Greene, and A. I. Meyers, *J. Heterocyclic Chem.* **1**, 300 (1964).

^{117b} Private communication from Professor A. I. Meyers, Louisiana State University, New Orleans, 1965.

^{117c} R. E. Lyle, R. Munk, and L. Ladd, *J. Org. Chem.* **30**, 293 (1965).

^{117d} J. O. Jilek, J. Pomykacěk, J. Metyšova, J. Metyš, and M. Protira, *Collection Czech. Chem. Commun.* **30**, 463 (1965).

^{117e} T. Miyadera and Y. Kishida, *Tetrahedron Letters*, No. 14, 905 (1965).

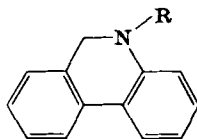
¹¹⁸ W. C. Wooten and R. L. McKee, *J. Am. Chem. Soc.* **71**, 2946 (1949).

^{118a} P. DeMayo and W. Rigby, *Nature* **166**, 1075 (1950).

¹¹⁹ G. M. Badger, J. H. Seidler, and B. Thomson, *J. Chem. Soc.* **1951**, 3207.

¹²⁰ P. Karrer, L. Szabo, H. J. V. Krishna, and R. Schwyzler, *Helv. Chim. Acta* **33**, 294 (1950).

dithionite for this reduction produced a different dihydrophenanthridine, for which the structure, *N,N*-dimethyl-5,6,5',6'-tetrahydro-6,6'-diphenanthridyl, was suggested by the experimental evidence.^{120a}

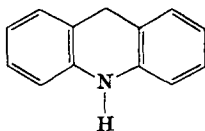


(90)

B. ACRIDINE

In a study of the lithium aluminum hydride reduction of a series of nitrogen aromatic heterocyclics, Bohlmann⁹⁷ found that this metal hydride effected a conversion of acridine to 9,10-dihydroacridine (**91**) in high yield and purity. The ultraviolet spectrum of the isolated dihydroacridine (λ_{max} 288 $\text{m}\mu$, $\log \epsilon = 4.18$) was confirmed by Braude *et al.*⁹² as a part of a study of the hydride donor properties of a series of aromatic nitrogen-heterocycles. These workers found that the dihydroacridine underwent a slow oxidation to acridine in air and a rapid hydrogen transfer in the presence of chloranil to form the quinol and acridine. The dihydroacridine was, however, quite stable under dry nitrogen.

Acridine and 9,10-dihydroacridine (**91**) form bright yellow complexes; however, such complexes have not been observed as direct reduction products of the metal hydride reduction of acridine.



(91)

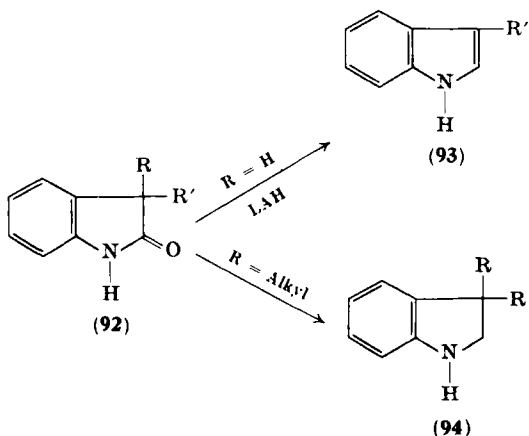
C. INDOLE RING SYSTEM

1. Indole and Oxindole

The heterocyclic ring of indole is not subject to nucleophilic attack and undergoes no reduction with lithium aluminum hydride or

^{120a} P. R. Brook, F. Blumer, H. J. V. Krishna, S. Schnell, and P. Karrer, *Helv. Chim. Acta* **39**, 667 (1956).

sodium borohydride. The non-aromatic 3-*H*-indole (indolenine), however, is converted to the indoline by these reagents.^{104, 121} The stability of the indole ring to LAH provided a method for determining the degree of substitution at the 3-position of oxindoles (92). The lactam function of (92) undergoes reduction with LAH and eliminates water to give an indole (93) if a single substituent is at the 3-position, whereas an indoline (94) is obtained from a 3,3-disubstituted oxindole.¹²²⁻¹²⁶



2. Tetrahydrocarbazole

Cerutti and Schmid¹⁰⁵ employed the principles of metal hydride reduction as a structural confirmation for the products obtained from the photo-reduction of a series of indolenine type compounds. The reduction product of 9,4a-diethyl-1,2,3,4-tetrahydrocarbazolinium chloride (95) with sodium borohydride was found to be identical with the photo-reduction product obtained from mercury sensitized irradiation of 95, confirming the structure of the product as 96.

Reduction of 4a-methyl-1,2,3,4-tetrahydro-4a-*H*-carbazole (84) by the use of lithium aluminum hydride gave a product (85) which was

¹²¹ B. Witkop and J. B. Patrick, *J. Am. Chem. Soc.* **75**, 4474 (1953).

¹²² B. Witkop, *J. Am. Chem. Soc.* **70**, 1424 (1948).

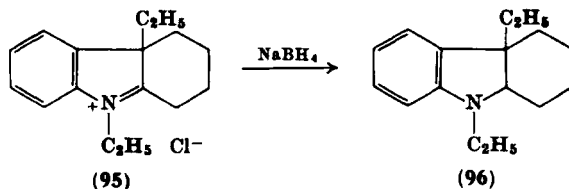
¹²³ T. S. Stevens, in "Recent Work on Naturally-Occurring Nitrogen Heterocyclic Compounds," Spec. Publ. No. 3, p. 23. Chem. Soc., London, 1955.

¹²⁴ R. Goutarel, M. Janot, V. Prelog, R. Sneed, and W. Taylor, *Helv. Chim. Acta* **34**, 1139 and 1962 (1951).

¹²⁵ J. C. Seaton and L. Marion, *Can. J. Chem.* **35**, 1102 (1957).

¹²⁶ J. C. Seaton, R. Tondeur, and L. Marion, *Can. J. Chem.* **36**, 1031 (1958).

identical with one of the products obtained from the irradiation of **84**. The reduction process has thus been used as a basis for structural assignments of products obtained from photochemical transformations.

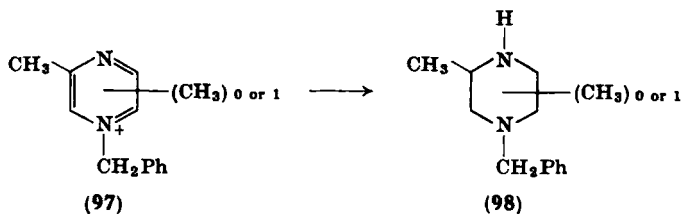


VII. Reduction of Heterocycles Containing Two Nitrogen Atoms

A. 1,4-DIAZINES

1. *Pyrazinium Salts*

The reduction of the benzyl bromide quaternary salts of mono- and dimethylpyrazines (**97**) with sodium borohydride in aqueous medium produced the corresponding piperazines (**98**). The changes in the ultraviolet absorption spectrum which occurred during the reduction clearly showed that a dihydropyrazine was formed as an intermediate. Gas chromatographic analysis of the piperazine from the 3,5-dimethyl-derivative indicated the formation of a single geometric isomer, the *cis* (*vide infra*). The 2,5-dimethylpyrazinium salt gave two isomeric piperazines, the *trans*-isomer predominating.¹²⁷

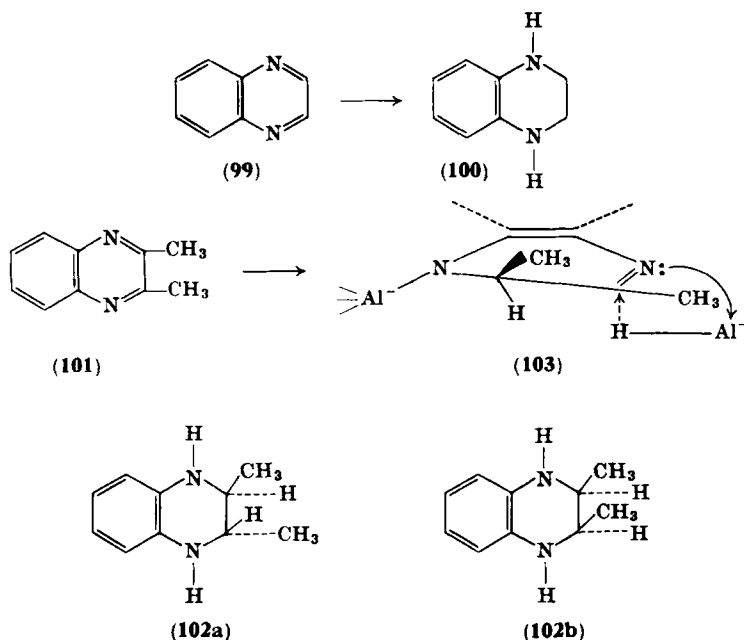


2. *Quinoxalines*

Bohlmann⁹⁷ reported that an ethereal solution of quinoxaline (**99**) on treatment with lithium aluminum hydride resulted in partial reduction of the nitrogenous heterocyclic ring, 1,2,3,4-tetrahydroquinoxaline (**100**) being the sole product of the reaction. Similar

¹²⁷ R. E. Lyle and J. J. Thomas, *J. Org. Chem.*, **30**, 1907 (1965).

treatment of 2,3-dimethylquinoxaline (**101**) was reported to give a good yield of a tetrahydroquinoxaline (**102**), m.p. 102–103°. Bohlmann presumed that this material was the *trans*-isomer (**102a**) on the basis of identity of melting point with the dimethyltetrahydroquinoxaline isolated by Bergstrom and Ogg¹²⁸ from treatment of quinoxaline with methylmagnesium iodide. The *trans*-configuration of the methyl groups in the Grignard product had been established by Bergstrom and Ogg as well as by Gibson.¹²⁹ In a reinvestigation of this metal hydride



reduction, DeSelms and Mosher¹³⁰ obtained only the *cis*-2,3-dimethyl-1,2,3,4-tetrahydroquinoxaline (**102b**), m.p. 113–114°. The fact that the *trans*-isomer did not rearrange to the *cis*-isomer under the reaction conditions indicated that the reduction was stereospecific. The stereospecificity of this reduction may be considered to be a consequence of a two-step reduction mechanism. After initial reduction of one carbon–nitrogen double bond, the second hydride ion probably is

¹²⁸ J. W. Bergstrom and R. A. Ogg, *J. Am. Chem. Soc.* **53**, 245 (1931).

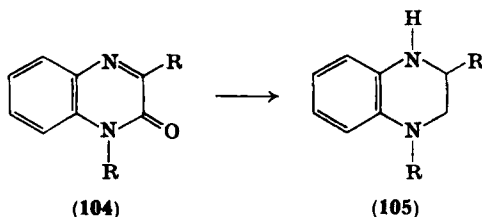
¹²⁹ C. S. Gibson, *J. Chem. Soc.* **1927**, 342.

¹³⁰ R. C. DeSelms and H. S. Mosher, *J. Am. Chem. Soc.* **82**, 3762 (1960).

transferred directly from the aluminohydride complex (103) to the least hindered side of the ring system. The stereochemical outcome of the reduction clearly indicates that a free hydride ion is not involved.¹³⁰

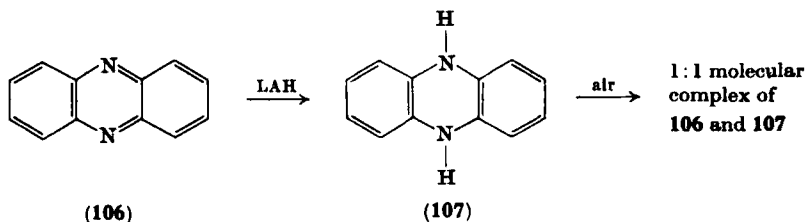
The reduction of 1-methyl- or ethyl-quinoxalium salts with aqueous sodium borohydride formed the 1-substituted-1,2,3,4-tetrahydroquinoxaline.¹³¹ The tetrahydroquinoxalines were the sole products and were obtained in good yield.

The reduction of a series of 1,3-disubstituted-2-oxo-1,2-dihydroquinoxalines (104) with lithium aluminum hydride to the corresponding 1,2,3,4-tetrahydroquinoxalines (105) has also been reported.¹³² Under mild reaction conditions an intermediate was isolated which retained a double bond in the ring, but the intermediate was not sufficiently stable to be characterized.



3. Phenazines

Birkofer and Birkofer¹³³ and Bohlmann⁹⁷ have independently reported that the lithium aluminum hydride reduction of phenazine (106) in cold ethereal solution leads initially to 9,10-dihydrophenazine (107) which readily undergoes aerial oxidation to a 1:1 molecular complex of phenazine and 9,10-dihydrophenazine. Birkofer and Birkofer were successful in isolating the dihydrophenazine (107) by



¹³¹ R. F. Smith, W. J. Rebel, and T. N. Beach, *J. Org. Chem.* **24**, 205 (1959).

¹³² J. Druey and A. Huni, *Helv. Chim. Acta* **35**, 2301 (1952).

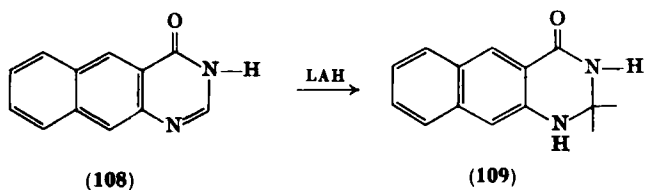
¹³³ L. Birkofer and A. Birkofer, *Ber.* **85**, 286 (1952).

carrying out the reduction and isolation in a nitrogen atmosphere. The reduction of 1-carbomethoxyphenazine to 1-phenazylmethanol with lithium aluminum hydride can be accomplished in low yield, presumably through reoxidation of the dihydrophenazine during the work-up of the reaction mixture.¹³³

B. 1,3-DIAZINES

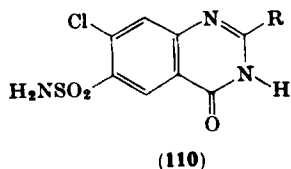
1. 1,3-Diazaanthracene

Treatment of an ethereal solution of 4-oxo-dihydro-1,3-diazaanthracene (**108**) with lithium aluminum hydride reportedly resulted in the reduction of only the 1,2-carbon-nitrogen double bond with 4-oxo-1,2,3,4-tetrahydro-1,3-diazaanthracene (**109**) being the only product isolated.¹³⁴ Apparently conditions were not sufficiently vigorous for the further reduction of the tautomeric form of **109**, or possibly the formation of a complex with the aluminohydride prevented attack at the 4-position.



2. Quinazolinone

The reduction of the 1,2-double bond in a series of 7-chloro-6-sulfamyl-4(3*H*)-quinazolinones (**110**) by sodium borohydride in the presence of aluminum trichloride has been reported.¹³⁵ Lithium aluminum hydride caused the conversion of 3-methyl-4(3*H*)-quinazolinone to 3-methyl-1,2,3,4-tetrahydroquinazoline.^{135a}



¹³⁴ A. Etienne and M. Legrand, *Compt. Rend.* **229**, 220 (1949).

¹³⁵ E. Cohen, B. Klarberg, and J. R. Vaughan, Jr., *J. Am. Chem. Soc.* **81**, 5508 (1959).

^{135a} A. R. Osborn and K. Schofield, *J. Chem. Soc.* **1956**, 3977.

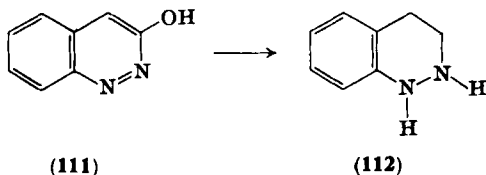
3. Quinazoline

The reduction of quinazoline with lithium aluminum hydride gave a mixture of 1,2,3,4-tetrahydroquinazoline and *N*^α-methyl-α,2-toluenediamine. 4-Aryloxy- and 4-alkoxy-quinazolines gave 1,2-dihydro derivatives, while 2-chloro-4-phenyl- and 4-chloro-2-phenyl-quinazolines gave the corresponding 3,4-dihydroquinolines with reductive loss of halogen.^{135b}

C. 1,2-DIAZINES

1. Cinnoline

The chemical reductions of cinnolines quite frequently lead to indole derivatives, although di- and tetrahydrocinnolines have been isolated in some cases.¹³⁶ Ames and Kucharska¹³⁷ recently found that the parent tetrahydro compound, 1,2,3,4-tetrahydrocinnoline (**112**), can be obtained readily as one of the products of the lithium aluminum hydride reduction of 3-hydroxycinnoline (**111**) in refluxing 1,2-dimethoxyethane. 3-Hydroxycinnoline (**111**) can be regarded as the tautomeric form of an amide. The reduction of 4-hydroxycinnoline and 4-methoxycinnoline reportedly gave mixtures of cinnoline and 1,2,3,4-tetrahydrocinnoline, whereas treatment of 4-chlorocinnoline with lithium aluminum hydride gave 4,4-bicinnolinyl as the only product isolated.¹³⁷



The alkylation of 3- or 4-hydroxycinnolines has been shown to occur at the 2-position. Reduction of these cinnolinium salts with lithium aluminum hydride gave 2-alkyl-1,2,3,4-tetrahydrocinnolines which darkened rapidly on exposure to air but could be converted to stable derivatives.^{137a,b}

^{135b} R. F. Smith, P. C. Briggs, R. A. Kent, J. A. Albright, and E. J. Walsh, *J. Heterocyclic Chem.* **2**, 157 (1965).

¹³⁶ T. L. Jacobs, in "Heterocyclic Compounds" (R. C. Elderfield, ed.), Vol. VI, p. 159. Wiley, New York, 1957.

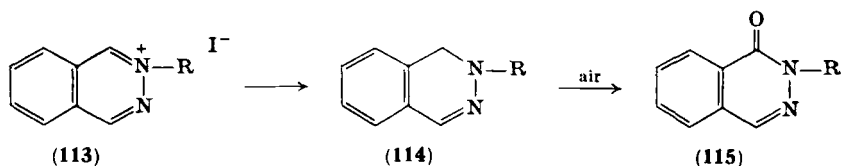
¹³⁷ D. E. Ames and H. Z. Kucharska, *J. Chem. Soc.* **1962**, 1509.

^{137a} D. E. Ames and H. Z. Kucharska, *J. Chem. Soc.* **1963**, 4924.

^{137b} D. E. Ames and H. Z. Kucharska, *J. Chem. Soc.* **1964**, 283.

2. Phthalazines

Smith and Otremba¹³⁸ have found that the sodium borohydride reduction of 2-methyl- and 2-ethyl-phthalazinium iodide (**113**) in aqueous medium results in good yields of the corresponding 1,2-dihydrophthalazines (**114**). The dihydrophthalazines were found to be stable to excess sodium borohydride in refluxing methanol but underwent a facile air oxidation to phthalazinones (**115**). The borohydride reduction of 2-benzyl-phthalazinium chloride proceeded with apparent partial debenzylation, for a 31% yield of the parent 1,2-dihydrophthalazine (**114**, R = H) was isolated as the 2,2-dimethyl quaternary salt.



D. TWO NITROGEN ATOMS IN DIFFERENT RINGS

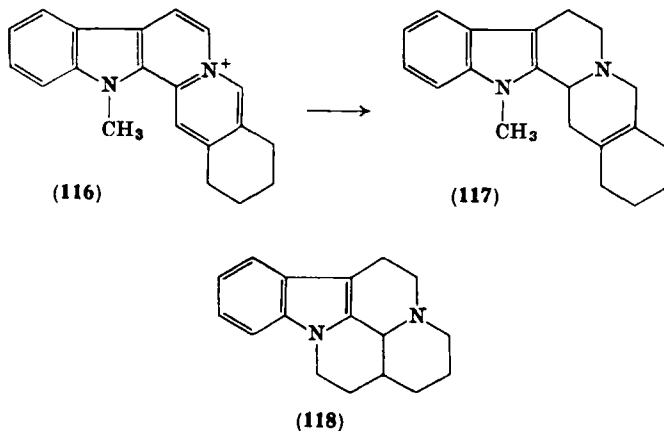
1. Carbolines

The reduction of both the α - and the β -carbolinium ring system by sodium borohydride in protonic medium results in the conversion of the α - or β -carbolinium ion to the corresponding 1,2,3,4-tetrahydro-carbolines¹³⁹ as would be expected by analogy to the reduction of pyridinium ions by this reagent (Section I). An early synthetic application of this reduction was reported by Witkop.⁷⁵ The conversion of methylsempervirine (**116**) to a hexahydrosempervirine (**119**) was effected in good yield by sodium borohydride in refluxing methanol. The assignment of the remaining isolated double bond to the $\Delta^{15,20}$ or $\Delta^{14,15}$ position was not clearly established. Recent investigations of the mechanism of the sodium borohydride reduction of pyridinium ions would suggest that the $\Delta^{15,20}$ isomer would be the most reasonable reduction product (see Section I). The sodium borohydride reduction of the β -carbolinium ring system was used by

¹³⁸ R. F. Smith and E. D. Otremba, *J. Org. Chem.* **27**, 879 (1962).

¹³⁹ A. P. Gray, E. E. Spinner, and C. J. Cavallito, *J. Am. Chem. Soc.* **76**, 2792 (1954).

Wieland and Neeb¹⁴⁰ for the synthesis of some pentacyclic analogs (118) of calabash curare.



2. Phenanthroline

Karrer²⁰ has reported the isolation of a dihydro-*p*-phenanthroline from the sodium borohydride reduction of *p*-phenanthroline methiodide (26). An isomeric dihydro-*p*-phenanthroline was isolated from the sodium dithionite reduction of this methiodide. The isomeric dihydro-*p*-phenanthrolines were found to give the same tetrahydro-*p*-phenanthroline on catalytic hydrogenation. On heating, the isomer obtained from the borohydride reduction was found to undergo a facile conversion to the dihydro-*p*-phenanthroline obtained from the dithionite reduction.

The fact that dithionite reduction normally results in 1,4-addition, while borohydride apparently prefers hydride attack adjacent to nitrogen, suggested that the borohydride product was a 1,2-dihydro-*p*-phenanthroline, and that the dithionite reduction product was the isomeric 1,4-dihydro-*p*-phenanthroline.

VIII. Reductions of Azoles

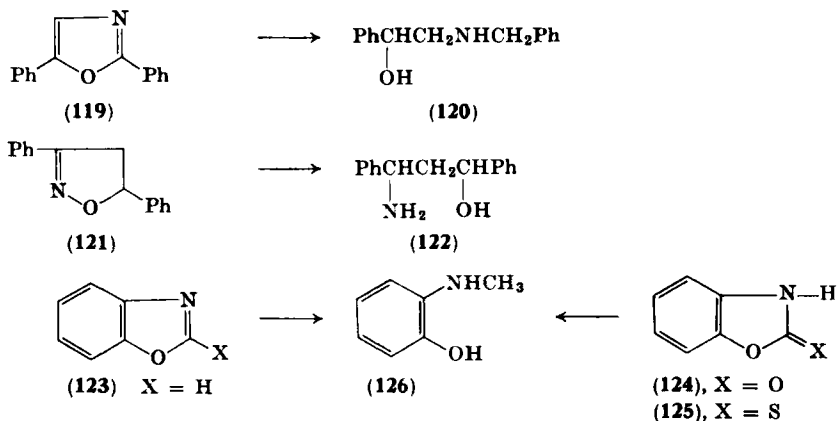
The azoles and benzazoles contain the hetero-nitrogen bonded in the same manner as pyridine, and thus reduction of the bases with lithium aluminum hydride or the salts with sodium borohydride

¹⁴⁰ T. Wieland and E. Neeb, *Ann.* **600**, 161 (1956).

would be expected. In general this is true, but the reduced forms of the heterocycles are often unstable to the conditions of the reactions, and isolation results in acyclic products.

A. OXAZOLES, ISOXAZOLES, AND THEIR POLYNUCLEAR DERIVATIVES

The tetrahydro-derivatives of the oxazole and isoxazole system are unstable. As a consequence, only acyclic products have been reported from the reductions with complex metal hydrides. 2,5-Diphenyl-oxazole (119) gave 2-benzylamino-1-phenylethanol (120),¹⁴¹ and 3,5-diphenyl-2-isoxazoline (121) was converted to 3-amino-1,3-diphenylpropanol (122)¹⁴² on reduction with lithium aluminum hydride. 3-Phenylbenzoxazole was resistant to reduction with lithium aluminum hydride and sodium borohydride,¹⁴³ but benzoxazole (123), benzoxazol-2-one (124), and benzoxazol-2-thione (125) have been reported¹⁴¹ to yield 2-methylaminophenol (126) on reduction with lithium aluminum hydride.



B. THIAZOLE AND ITS DERIVATIVES^{143a}

The reduction of the thiazolium salt, thiamine, has been investigated with sodium borohydride, trimethoxyborohydride, and lithium

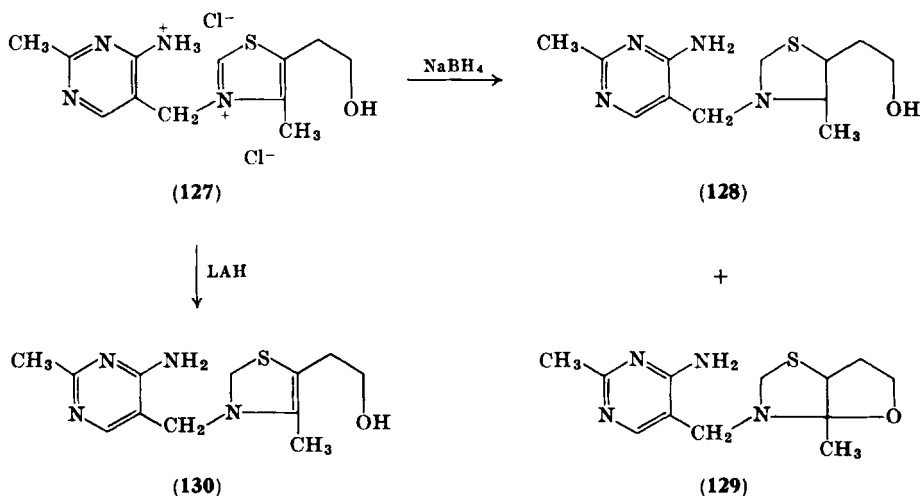
¹⁴¹ N. G. Gaylord and D. J. Kay, *J. Am. Chem. Soc.* **78**, 2167 (1956).

¹⁴² G. W. Perold and F. V. K. von Reiche, *J. Am. Chem. Soc.* **79**, 465 (1957).

¹⁴³ Private communication from Professor D. Nightingale, University of Missouri, Columbia, 1963.

^{143a} See *Added in Proof*, p. 93.

aluminum hydride. The reaction of thiamine chloride (**127**) with sodium borohydride in aqueous medium was shown to give the tetrahydrothiamine (**128**).^{144, 145} A second product (**129**) was reported by Bonvicino and Hennessy.¹⁴⁴ The cyclization apparently occurred as a result of the alcoholic oxygen competing with the borohydride ion for attack on the protonated dihydro-intermediate (compare the cyclizations in Sections II, B and III, B). The reaction of thiamine chloride (**127**) with lithium aluminum hydride or sodium trimethoxyborohydride gave only dihydrothiamine (**130**).¹⁴⁶ (See also Section V.)



C. DERIVATIVES OF IMIDAZOLE AND BENZIMIDAZOLE

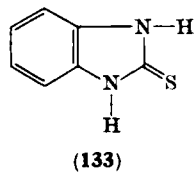
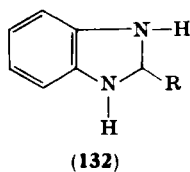
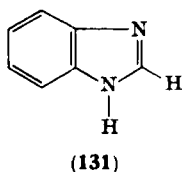
The bonding to form the imidazole ring would suggest that reduction with complex metal hydrides should be possible. Lithium aluminum hydride, however, would be expected to undergo an acid-base reaction with the N—H of the 1-position forming the anion of imidazole which would resist further attack by complex hydride ions. Such observations were made by Bohlmann⁹⁷ with benzimidazole (**131**). Thus at room temperature or below only salt formation was observed on reaction of lithium aluminum hydride with benzimidazole

¹⁴⁴ G. F. Bonvicino and D. J. Hennessy, *J. Am. Chem. Soc.* **79**, 6325 (1957).

¹⁴⁵ H. Hirano, *Yakugaku Zasshi* **78**, 1387 (1958); *Chem. Abstr.* **53**, 8145 (1959).

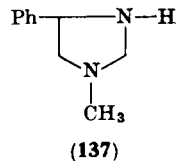
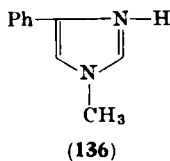
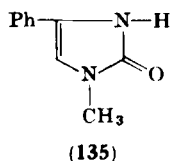
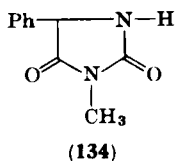
¹⁴⁶ P. Karrer and H. Krishna, *Helv. Chim. Acta* **33**, 555 (1950).

(131). With benzene-ether as solvent, the reaction gave dihydrobenzimidazole (132), which was isolated as the picrate.



Benzimidazole-2-thione (133) has been reported to give no reaction with lithium aluminum hydride.¹⁴¹ There are two potentially acidic hydrogens in 133, and the increased nucleophilicity of the ring system due to salt formation probably accounts for the failure of reaction.

The reaction of hydantoins (tautomers of 2,4-dihydroxyimidazoles) with lithium aluminum hydride has been reported to give imidazolones, imidazoles, or imidazolidines depending upon the conditions of the reaction.¹⁴⁷ 1-Methyl-4-phenylhydantoin (134) with LAH at room temperature gave 1-methyl-4-phenyl-2-imidazolone (135), which was converted on prolonged treatment with LAH to 1-methyl-4-phenylimidazole (136). The vigorous reaction of 134 with excess LAH was reported to give 1-methyl-4-phenylimidazolidine (137).



IX. Reduction of Heterocycles Containing Three Nitrogen Atoms

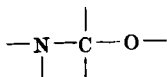
A. TRIAZOLES

The reduction of 1-hydroxymethyl- and 1-benzoyloxymethyl-benzotriazole (138) with lithium aluminum hydride and sodium borohydride has been investigated by Gaylord and Kay.¹⁴⁸ The hydroxymethyl compound failed to undergo reduction with lithium aluminum hydride, apparently as a result of the immediate formation of an insoluble complex by reaction of the metal hydride with the

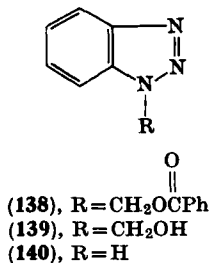
¹⁴⁷ I. Wilk and W. Close, *J. Org. Chem.* **15**, 1020 (1950).

¹⁴⁸ N. G. Gaylord and D. J. Kay, *J. Org. Chem.* **23**, 1574 (1958).

active hydrogen of the benzotriazole. The benzoyloxymethyl-derivative, however, was reduced to a mixture of benzyl alcohol (93%), 1-hydroxymethyl-benzotriazole **139** (17%), and benzotriazole **140** (47%). The isolation of the last compound indicated that this reduction was unique in that the cleavage of the



group occurred at the carbon-nitrogen bond instead of at the carbon-oxygen bond. None of the expected 1-methyl-benzotriazole which would have resulted from cleavage of the carbon-oxygen bond was observed. It was suggested that the observed cleavage reaction was the result of a direct displacement of carbon effected by hydride attack on nitrogen, the nitrogen being the more positive center in this system due to its presence in the benzotriazole ring system.



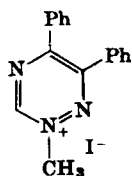
The sodium borohydride reduction of benzotriazoles **138** and **139** gave, in good yield, benzotriazole **140**. The cleavage of the carbon-nitrogen bond by the complex hydride thus occurred in preference to reduction of the ring or carbon-oxygen bond cleavage.

B. TRIAZINES

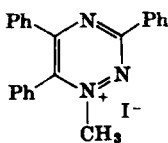
Atkinson and Cossey¹⁴⁹ reported that the reduction of 2-methyl-5,6-diphenyltriazinium iodide (**141**) with potassium borohydride in methanol led to a tetrahydro-2-methyl-5,6-diphenyl-1,2,4-triazine. The ultraviolet absorption spectrum of this tetrahydro-1,2,4-triazine showed a maximum at 297 mμ (log ε = 4.06). A similar reduction of 1-methyl-3,5,6-triphenyl-1,2,4-triazinium iodide (**142**) gave a dihydro-1,2,4-triazine, the ultraviolet spectrum of which had maxima at 273 mμ (log ε = 4.46) and 410–420 mμ (log ε = 3.62). No assignment of

¹⁴⁹ C. M. Atkinson and H. D. Cossey, *J. Chem. Soc.* **1963**, 1628.

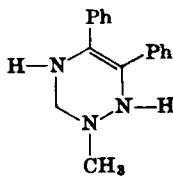
structures of these partially reduced triazines was made on the basis of these limited data, but in consideration of the path of reduction of other heterocycles, one might speculate that the tetrahydro-derivative was **143** and that the dihydro-product from **142** had the structure **144**.



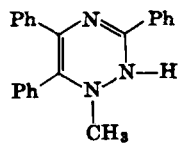
(141)



(142)



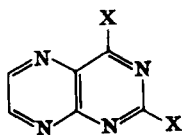
(143)



(144)

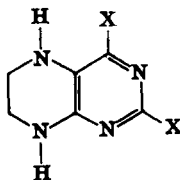
X. Reduction of Pteridines with Complex Metal Hydrides

The pteridine ring system is composed of fused pyrazine and pyrimidine rings, either of which might be attacked by a complex metal hydride. The reaction of pteridine (**145**), 2,4-dichloropterin (**146**), or 2,4-dimethoxypteridine (**147**) with lithium aluminum hydride was reported to occur with reduction of the pyrazine ring to give the 5,6,7,8-tetrahydropteridine (**148–150**, respectively).¹⁵⁰



(145), X = H

(146), X = Cl

(147), X = OCH₃

(148), X = H

(149), X = Cl

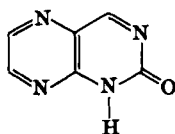
(150), X = OCH₃

The product of the reaction of sodium or potassium borohydride with substituted pteridines is highly sensitive to the location of the substituent. Thus, Albert and Matsuura¹⁵¹ reported the formation of 2-oxo-1,2,3,4-tetrahydropteridine (**152**) from the reaction of potassium borohydride with pteridin-2-one (**151**). This appears to be the only example of attack of the pyrimidine ring of pteridines by complex metal hydrides. The same dihydropteridine (**152**) was formed by reduction of **151** with hydrosulfite ion, and the structure of the product of the latter reaction was elegantly proved using deuterium

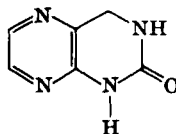
¹⁵⁰ E. C. Taylor and W. R. Sherman, *J. Am. Chem. Soc.* **81**, 2464 (1959).

¹⁵¹ A. Albert and S. Matsuura, *J. Chem. Soc.* **1961**, 5131.

tagging. It is interesting to note that reduction of **151** is possible only in basic medium, for in neutral solution the 3,4-double bond of **151** is hydrated.¹⁵¹

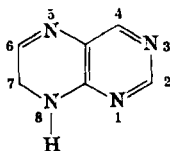


(151)

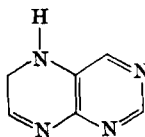


(152)

Oxo-groups located at other positions on the pteridine ring were shown by Albert and Matsuura¹⁵² to affect the structure of the dihydropteridine formed. Thus, pteridin-4- and 6-ones and 2,6- and 4,6-diones were converted to the corresponding 7,8-dihydro-derivatives (**153**), whereas pteridin-7-one and 4,7-dione formed the corresponding 5,6-dihydro-derivatives (**154**) on reaction with potassium borohydride.

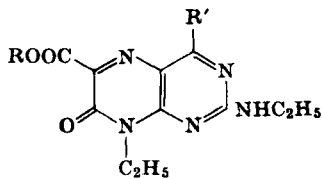


(153)

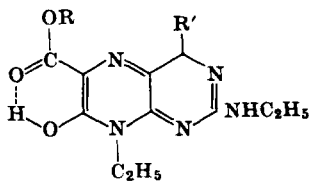


(154)

The reaction of derivatives of 2-ethylamino-8-ethyl-7-pteridinone carboxylic acid (**155**) with sodium borohydride gave the corresponding 4,8-dihydropteridine¹⁵³ (**156**). The original assignment of the 5,8-dihydro-structure¹⁵³ was revised on the basis of NMR studies of the reduction products.¹⁵⁴



(155)



(156)

¹⁵² A. Albert and S. Matsuura, *J. Chem. Soc.* **1962**, 2162.

¹⁵³ W. Pfeleiderer and E. C. Taylor, *J. Am. Chem. Soc.* **82**, 3765 (1960).

¹⁵⁴ E. C. Taylor, in "Pteridine Chemistry" (W. Pfeleiderer and E. C. Taylor, eds.), p. 209. Macmillan (Pergamon), New York, 1964.

XI. Summary

Nitrogen heterocycles more electrophilic than benzene are susceptible to attack by hydride ion from a complex metal hydride anion. In protic solvents the intermediate cyclic enamines can undergo further reduction. The proper choice of reducing agent and reaction conditions thus allows the preparation of many partially reduced nitrogen heterocycles unavailable by other routes. These reduction procedures provide a valuable adjunct to catalytic hydrogenation¹⁵⁵ for the syntheses of saturated nitrogen heterocycles.

Added in Proof

The reduction of pyridine with trimethylsilane and hydrolysis of the resulting 1-trimethylsilyl intermediate has been reported as a route to unsubstituted 1,4-dihydropyridine.¹⁵⁶ The reduction has been shown to be reversible at higher temperatures leading to an equilibrium mixture of dihydropyridines.¹⁵⁷

A systematic study of the reduction of thiazolium salts by complex metal hydrides has been promised in a preliminary communication on the mechanism of the reduction with sodium borohydride. The formation of 3-benzyl-4-methylthiazolidine from the reaction of 3-benzyl-4-methylthiazolium bromide and sodium borohydride was shown to occur in a manner similar to the reduction of pyridinium ions.¹⁵⁸

¹⁵⁵ M. Freifelder, *Advan. Catal.* **14**, 203 (1963).

¹⁵⁶ N. C. Cook and J. E. Lyons, *J. Am. Chem. Soc.* **87**, 3283 (1965).

¹⁵⁷ N. C. Cook and J. E. Lyons, Abstracts of the 150th Meeting of the American Chemical Society, Atlantic City, New Jersey, September, 1965, p. 24s.

¹⁵⁸ G. M. Clarke and P. Sykes, *Chem. Commun.* No. 15, 11 (1965).

Heterocyclic Syntheses Involving Nitrilium Salts and Nitriles under Acidic Conditions

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I. Introduction

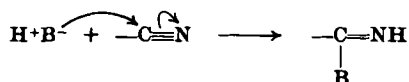
In the realm of synthetic heterocyclic chemistry the successful synthesis of a large variety of structures from nitriles has been due mainly to basic reagents or conditions. A brief survey of the available compendia^{1, 2} on the subject amply verifies this view. This situation has led to quite a thorough understanding of those reactions which involve nucleophilic attack on the nitrile function itself. The attack takes place on the carbon atom of the nitrile group, by virtue of the latter's high dipole moment (3.44–3.65 D in liquid media³), as shown in Eq. (1). It is this type of bond formation (i.e., B—C) which has been

¹ A. Weissberger (ed.), 21 vols. "The Chemistry of Heterocyclic Compounds." Wiley (Interscience), New York, 1950–1965.

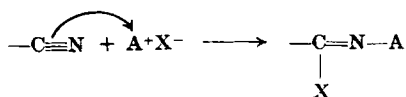
² R. C. Elderfield (ed.), 7 vols. "Heterocyclic Compounds." Wiley, New York, 1950–1961.

³ E. G. Cowley and J. R. Partington, *J. Chem. Soc.* **1935**, 604.

utilized so often in heterocyclic syntheses. The reaction has the advantage of generating an imine function which is available for further ring closure.



The direct use of the nucleophilic properties of the nitrile group in syntheses of this kind has, however, had its advent only recently. Here the bond formation takes the generalized form:



Whereas the value of this reaction lies in the forging of the N—A bond, the importance of the C—X bond formation cannot be overlooked since it is often intrinsically necessary in heterocycle formation. It is with reactions of type (2) that this chapter deals. The only previous review article pertaining to this subject is that of E. N. Zil'berman⁴ which does not deal with heterocyclic syntheses specifically. Recent advances justify a new review of the latter area. Principally, the use of three types of reactions are discussed: (a) the Ritter reaction; (b) reactions involving nitrilium salts; and (c) α,ω -dinitrile cyclizations. All appear to be variations of the above theme.

II. Ring Formation Involving a Mononitrile Component

The heterocyclic syntheses that can be accomplished using a mononitrile are of the more conventional type where, generally, two organic components are combined to produce the ring.

The first of these approaches stems from the Ritter reaction, whereas the second utilizes nitrilium salt intermediates. These reactions are probably different in degree rather than in kind since they are regarded as involving similar intermediates.

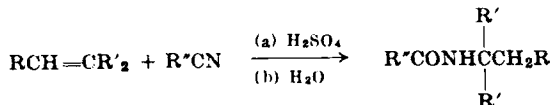
A. THE RITTER REACTION

In 1948 Ritter⁵ described a new reaction in which N-substituted amides were prepared from alkenes and nitriles in the presence of a

⁴ E. N. Zil'berman, *Russ. Chem. Rev. (Engl. Transl.)* **29**, 311 (1960).

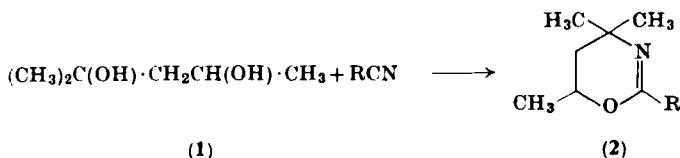
⁵ J. J. Ritter and P. P. Minieri, *J. Am. Chem. Soc.* **70**, 4045 (1948).

large excess of concentrated sulfuric acid. The reaction has since been studied extensively⁶⁻⁸ and, besides alkenes, it was found possible to utilize secondary and tertiary alcohols. Recently, the reaction has been applied to the synthesis of heterocyclic substances.



1. 5,6-Dihydro-1,4-oxazines and 2-Oxazolines

One of the earliest heterocyclic applications of the Ritter reaction was to the synthesis of dihydro-1,3-oxazines.⁹ It was found that the reaction of the dialcohol (1) with nitriles leads to the oxazines (2) rather than the expected bis-amides (Table I). The yields are only fair



(26–72%) but its experimental convenience makes it superior to previous methods¹⁰ for the preparation of this class of compounds. α,ω -Dinitriles behave in a similar way, affording the α,ω -bis-heterocyclyl alkanes,¹¹ although if a large excess of the dinitrile is used, reaction can be restricted to one end of the chain.¹²

The application of this approach to the synthesis of five-membered rings from 1,2-dihydroxy compounds does not appear to have been

⁶ F. R. Benson and J. J. Ritter, *J. Am. Chem. Soc.* **71**, 4128 (1949).

⁷ L. W. Hartzel and J. J. Ritter, *J. Am. Chem. Soc.* **71**, 4130 (1949).

⁸ For a review of the reaction, see F. Möller in "Methoden der organischen (J. Houben and T. Weyl, eds.), Vol. 11, Part 1, p. 994. Thieme, Stuttgart, 1957. An excellent list of later literature appears in C. H. Eugster, L. Lechner, and E. Jennig, *Helv. Chim. Acta* **46**, 543 (1963).

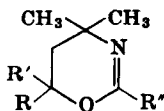
⁹ E. J. Tillmanns and J. J. Ritter, *J. Org. Chem.* **22**, 839 (1957).

¹⁰ N. H. Cromwell, in "Heterocyclic Compounds" (R. C. Elderfield, ed.), Vol. 6, Chapter II. Wiley, New York.

¹¹ A. I. Meyers, *J. Org. Chem.* **25**, 2231 (1960).

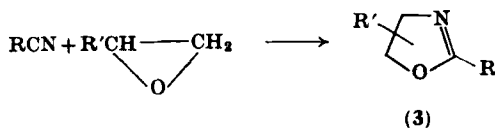
¹² A. I. Meyers, *J. Org. Chem.* **25**, 145 (1960).

TABLE I
PREPARATION OF 5,6-DIHYDRO-1,3-OXAZINES



| Nitrile | R | R' | R'' | Yield (%) | Reference |
|--|----------------|--------|---------------|-----------|-----------|
| CH ₃ CN | H | Methyl | Methyl | 44 | 9 |
| CH ₂ =CHCN | H | Methyl | Vinyl | 47 | 13 |
| CH ₂ =C(CH ₃)CN | H | Methyl | Isopropenyl | 53 | 13 |
| C ₆ H ₅ CN | H | Methyl | Phenyl | 47 | 9 |
| C ₆ H ₅ CH ₂ CN | H | Methyl | Benzyl | 26 | 9 |
| NC(CH ₂) ₂ CN | H | Methyl | 2-Cyanoethyl | 40 | 12 |
| | | | 1,2-Ethanebis | 53 | 11 |
| NC(CH ₂) ₄ CN | H | Methyl | 1,4-Butanebis | 47 | 11 |
| CH ₃ CN | Tetramethylene | | Methyl | 63 | 14 |
| C ₂ H ₅ CN | Tetramethylene | | Ethyl | 58 | 14 |
| CH ₂ =CHCN | Tetramethylene | | Vinyl | 57 | 14 |
| C ₆ H ₅ CN | Tetramethylene | | Phenyl | 72 | 14 |

tried. However, Oda *et al.*¹⁵ have reported recently that 1,2-epoxides will participate in the Ritter reaction to give 2-oxazolines (3). The yields are generally very low and the value of the reaction is further



reduced because mixtures are obtained in all cases except where R = H. The use of 1,3- or 1,4-epoxides in this reaction has not been attempted, but since these components do have ring strain,¹⁶ it is to be expected that they would yield the corresponding heterocycles.

¹³ J. W. Lynn, *J. Org. Chem.* **24**, 711 (1959).

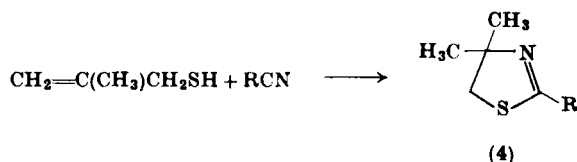
¹⁴ A. I. Meyers, J. Schneller, and N. K. Ralhan, *J. Org. Chem.* **28**, 2944 (1963).

¹⁵ R. Oda, M. Okano, S. Tokiura, and F. Misumi, *Bull. Chem. Soc. Japan* **35**, 1219 (1962); *Chem. Abstr.* **57**, 12453 (1962).

¹⁶ F. S. Dainton, K. J. Ivin, and D. A. G. Walmsley, *Trans. Faraday Soc.* **56**, 1784 (1960).

2. 2-Thiazolines, 5,6-Dihydro-1,3-thiazines, and 1,3-Thiazoles

In 1958 the extension of this reaction to the preparation of 2-thiazolines (4), using methallyl mercaptan, was reported.¹⁷ However,



Meyers¹⁸ subsequently found that the yields of 4 could be improved markedly by substituting 2-methyl-2-hydroxypropanethiol for methallyl mercaptan. He also extended the reaction to include certain dihydrothiazines (5) by means of 3-hydroxy-3-methylbutanethiol. Here, even when such diverse nitriles as acrylonitrile or *p*-aminobenzonitrile are used, yields of 5 approximate 50% (Table II).

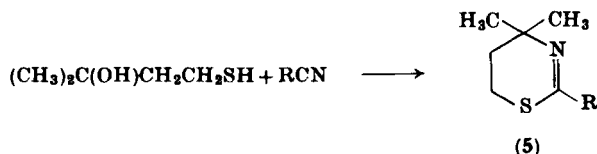


TABLE II
2-SUBSTITUTED 4,4-DIMETHYL-2-THIAZOLINES and
2-SUBSTITUTED 4,4-DIMETHYL-5,6-DIHYDRO-1,3-
THIAZINES¹⁸

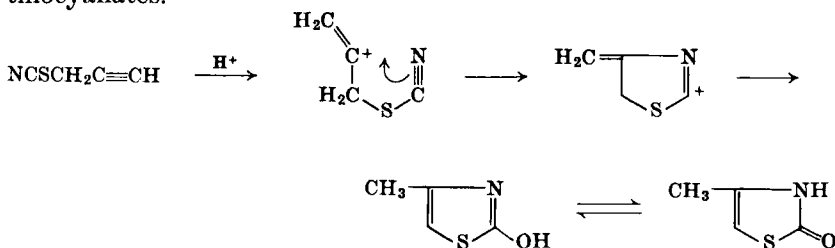
| Nitrile | 2-Substituent | Yield (%) |
|--|---------------|-----------|
| <i>Thiazolines</i> | | |
| CH ₃ CN | Methyl | 50 |
| CH ₂ =CHCN | Vinyl | 47 |
| C ₆ H ₅ CN | Phenyl | 51 |
| 4-NH ₂ C ₆ H ₄ CN | 4-Aminophenyl | 55 |
| <i>Dihydrothiazines</i> | | |
| HCN | None | 42 |
| CH ₃ CN | Methyl | 41 |
| C ₂ H ₅ CN | Ethyl | 46 |
| CH ₂ =CHCN | Vinyl | 51 |
| C ₆ H ₅ CN | Phenyl | 48 |
| 4-CH ₃ C ₆ H ₄ CN | 4-Tolyl | 50 |
| 2-CH ₃ C ₆ H ₄ CN | 2-Tolyl | 45 |
| 4-NH ₂ C ₆ H ₄ CN | 4-Aminophenyl | 53 |

¹⁷ A. I. Meyers and J. J. Ritter, *J. Org. Chem.* **23**, 1918 (1958).

¹⁸ A. I. Meyers, *J. Org. Chem.* **25**, 1147 (1960).

Again α,ω -dinitriles lead to the corresponding α,ω -bis-heterocyclized alkanes.¹¹

A novel application of the Ritter reaction to the synthesis of 2-hydroxythiazoles was reported recently by Yura,¹⁹ using acetylenic thiocyanates.



The method, however, does not seem to be generally applicable.

3. 1-Pyrrolines and 5,6-Dihydropyridines

The most useful application of the Ritter reaction in heterocyclic synthesis appears to be the preparation of 1-pyrrolines¹⁷ (7). These

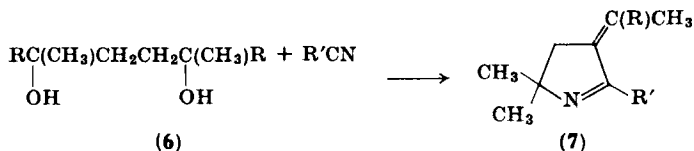
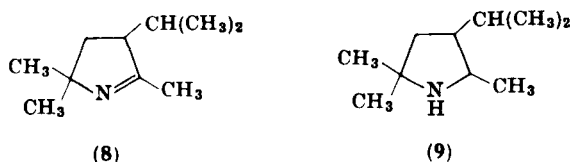


TABLE III
PREPARATION OF 1-PYRROLINES (7)

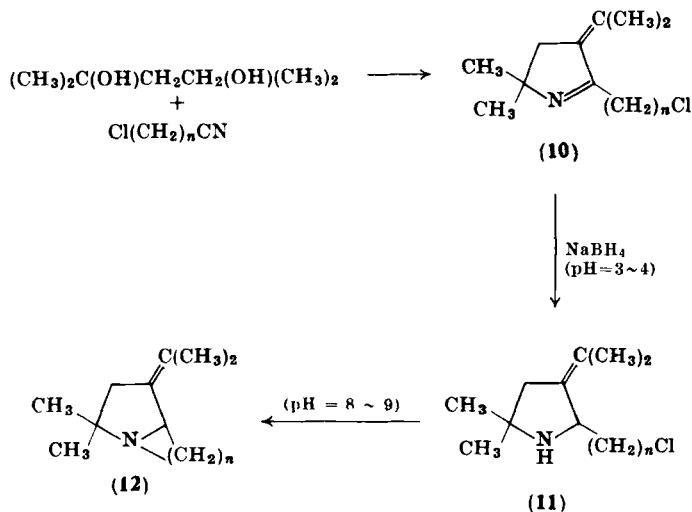
| Nitrile | R | R' | Yield (%) | Reference |
|---|--------|-----------------------|------------|-----------|
| CH ₃ CN | Methyl | Methyl | 80 | 17 |
| CH ₂ =CHCN | Methyl | Vinyl | 78 (crude) | 17 |
| C ₆ H ₅ CN | Methyl | Phenyl | 72 | 17 |
| 4-NO ₂ C ₆ H ₄ CN | Methyl | 4-Nitrophenyl | 78 | 17 |
| 4-CH ₃ OC ₆ H ₄ CN | Methyl | 4-Methoxyphenyl | 71 | 17 |
| 3-Pyridyl cyanide | Methyl | 3-Pyridyl | 62 | 17 |
| 4-Pyridyl cyanide | Methyl | 4-Pyridyl | 55 | 17 |
| CH ₃ CN | Ethyl | Methyl | 56 | 17 |
| NC(CH ₂) ₂ CN | Methyl | 1,2-Ethanebis- | 72 | 11 |
| NC(CH ₂) ₃ CN | Methyl | 1,3-Propanebis- | 76 | 11 |
| NC(CH ₂) ₄ CN | Methyl | 1,4-Butanebis- | 74 | 11 |
| O(CH ₂ CH ₂ CN) ₂ | Methyl | 3-Oxapentane-1,5-bis- | 64 | 11 |

¹⁹ Y. Yura, *Chem. Pharm. Bull. (Tokyo)* **10**, 1094 (1962).

materials can be obtained simply and in good yield (55–80%) from 1,4-glycols (6) (Table III). A limitation appears to be that R must be an alkyl (or aryl) group rather than hydrogen for good yields. However, the nature of R' does not appear to be a major factor since the reaction works well when R' is methyl, vinyl, or 4-pyridyl. The use of α,ω -dinitriles affords the expected α,ω -bis-heterocyclyl alkanes.¹¹ Hydrogenation of 7 (R = R' = CH₃) leads to either the di- (8) or tetrahydro derivative (9) in excellent yield.



The versatility of this approach was further expanded when Meyers and Libano^{20,21} showed that, using chloronitriles, azabicyclic compounds (12, $n = 2, 3$, or 4) can be obtained in good yields after two additional steps.

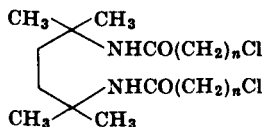


The synthesis²⁰ of a derivative of 1-azabicyclo[3.2.0]heptane (12, $n = 2$) by this method represents the first recorded example of this ring system. The reactions are generally carried out without

²⁰ A. I. Meyers and W. Y. Libano, *J. Org. Chem.* **26**, 1682 (1961).

²¹ A. I. Meyers and W. Y. Libano, *J. Org. Chem.* **26**, 4399 (1961).

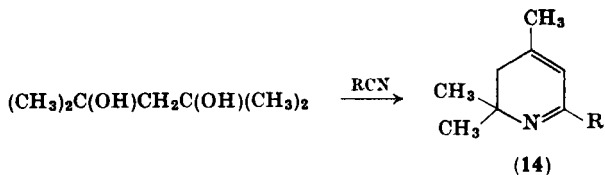
isolation of the intermediates **10** and **11**, but the large volume of solution necessarily involved is experimentally inconvenient. It stems from the relatively large quantities of sulfuric acid that must be neutralized after the formation of **10**. In an attempt partly to obviate this difficulty, Meyers used only half the quantity of sulfuric acid normally used in the Ritter reaction but only the diamide (**13**, $n = 2$) could be isolated (64% yield).



(13)

The extension of this synthesis to a wide variety of 1-azabicyclic compounds containing in some cases oxygen and sulfur atoms in the ring has been promised for future publications.

5,6-Dihydropyridines (**14**) were prepared by Meyers and Ritter¹⁷ in a fashion analogous to their preparation of 1-pyrrolines, viz.:



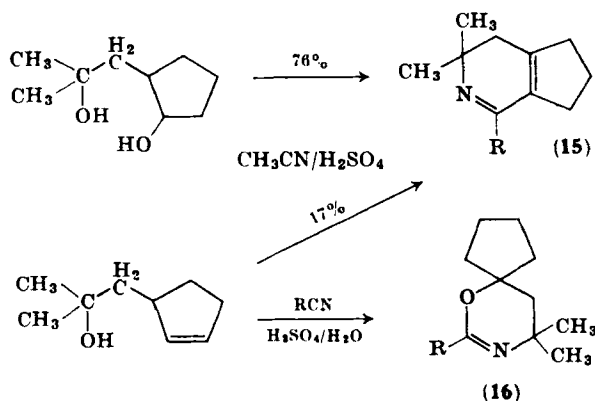
(14)

where R is methyl, vinyl, or phenyl.

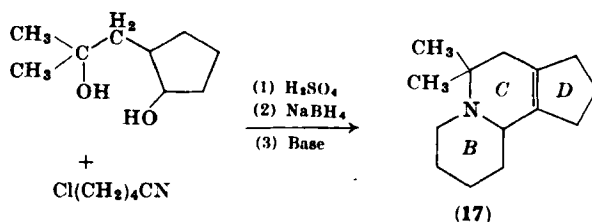
In all cases the yields are poor ($\sim 20\%$). Meyers *et al.*¹⁴, have recently followed this work up in an attempt to apply it to the synthesis of azasteroids. Their initial objective, that of obtaining a five-membered ring fused to a six-, was carried out as shown below and the product (**15**) represents a model for the C—D ring system of steroids.

Better yields of (**15**) are obtained from α -(2-hydroxycyclopentyl)-*tert*-butyl alcohol than from α -(3-cyclopentenyl)-*tert*-butyl alcohol, and in the latter case the reaction is complicated by the formation of (**16**). A study showed that (**16**) is the predominant product in more dilute sulfuric acid or when sulfuric acid is added to the mixture of the alkenol and acetonitrile.

Following the successful synthesis of (**15**), a variation of the synthesis of the bicyclic pyrrolines, mentioned above, was employed to



elaborate a tricyclic system (17).²² The route outlined below affords the final tricyclic compound in 46% over-all yield and represents the construction of rings *B*, *C*, and *D* of a 9-azasteroid nucleus.



The synthesis of homologs of this tricyclic compound in which ring *B* is four- or five-membered was also carried out, using the appropriate chloronitriles.²² The yields in these cases are somewhat better, being 50 and 54% respectively.

An unusual compound (18) was reported by Lora-Tamayo *et al.*²³ This they obtained from acetonitrile and 2,3-dimethylbutadiene, the only conjugated diene studied thus far. They presumed it arose via two Ritter reactions and a Diels-Alder reaction as shown below.

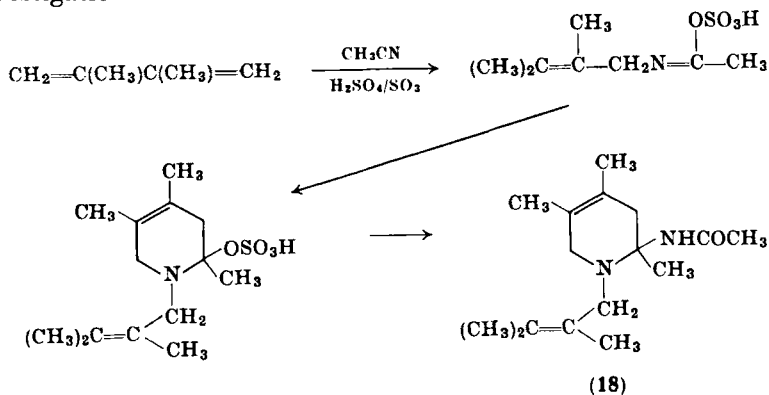
Despite the fact that the intermediates in this reaction are pictured by the authors as hydrogen sulfates, they perhaps would be better represented as the hydrogen sulfate salts of nitrilium and iminium ions, respectively.

Little evidence was offered in support of 18. The lack of formation

²² A. I. Meyers and N. K. Ralhan, *J. Org. Chem.* **28**, 2950 (1963).

²³ M. Lora-Tamayo, G. García Muñoz, and R. Madroño, *Bull. Soc. Chim. France* **1958**, 1334.

of acetone on chromic acid oxidation is noteworthy and further investigation seems desirable.



4. 3,4-Dihydroisoquinolines

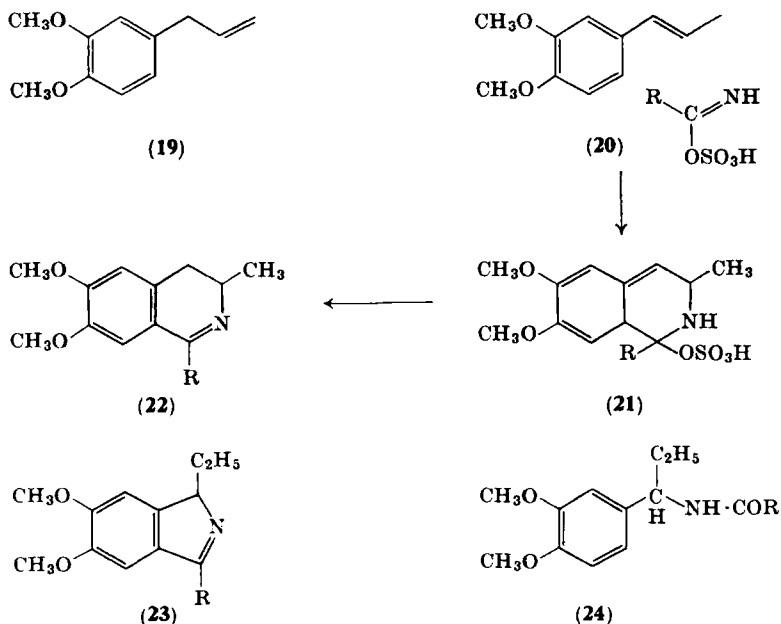
The first synthesis of a heterocyclic system (22) by the Ritter reaction was reported²⁴ in 1952, from the reaction of nitriles with methyleugenol (19). The reactions succeed only when the benzene ring is activated and allylbenzene itself gives the expected amide.

Lora-Tamayo *et al.*²³ prepared similar compounds from methylisoeugenol (20), using only one molar equivalent of sulfuric acid. They at first regarded the reaction as proceeding by a Diels-Alder reaction via 21, presumably since one might expect the formation of the five-membered ring (23) or the amide (24) if the initial stage were to follow the Ritter reaction. Alternatively, the reaction can be regarded as proceeding first by a Hoesch condensation of the nitrile with the benzene ring, followed by internal alkylation of the imine function by the propenyl group. The possibility that the products might arise by cyclization of nitrilium salts is considered again in Section II, B, 1. Subsequently, Lora-Tamayo's group developed much better methods for the preparation of these 3,4-dihydroisoquinolines. These also are discussed in the section on nitrilium salts.

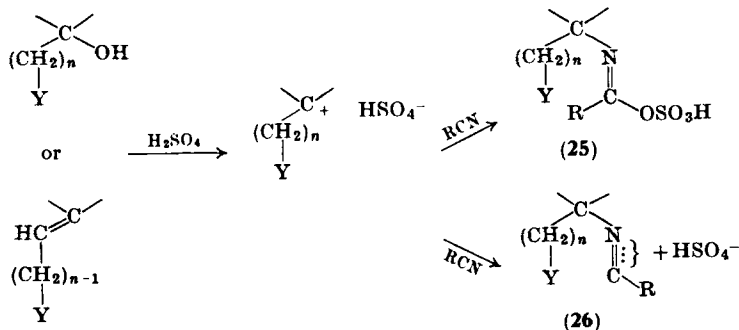
5. Mechanism of Reaction

The question of the mechanism of these reactions is still open because little work has been done in this direction. It seems unlikely, however, that one pathway will adequately describe all of the above cyclizations.

²⁴ J. J. Ritter and F. X. Murphy, *J. Am. Chem. Soc.* **74**, 763 (1952).

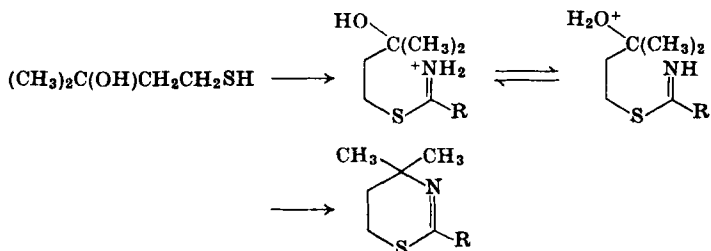


Ritter^{9,17} has expressed the view that the reactions involve the formation of a carbonium ion from the alcohol or alkene which subsequently *N*-alkylates the nitrile. The intermediate product was thought to be the imidol hydrogen sulfate (25) from which the hydrogen sulfate residue is displaced nucleophilically by the electron-rich group Y.

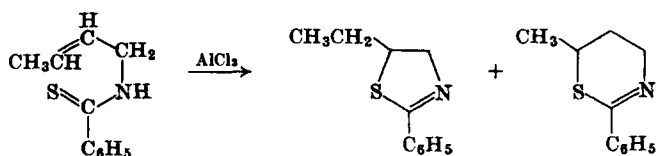


Meyers¹⁸ has pointed out that, alternatively, the nitrilium salt (26) may be the intermediate and that ring closure takes place by electrophilic attack on Y.

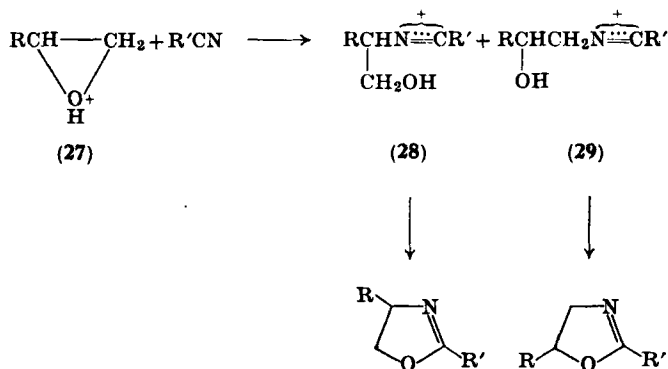
No credence appears to have been given to the view that in some cases, especially where $Y = SH$ or OH , the mechanism may follow the path exemplified below. This would be somewhat analogous to the



acid-catalyzed cyclization of *N*-alkenylthionamides to thiazolines and dihydrothiazines.²⁵



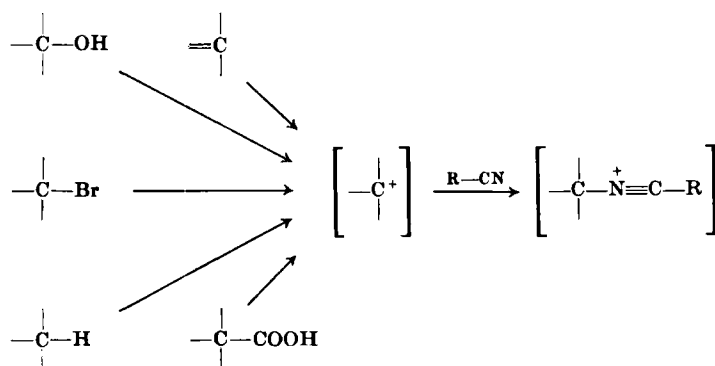
Again, since mixtures of 2-oxazolines are obtained from nitriles and unsymmetrical epoxides,¹⁵ it does not seem likely in this case that a purely carbonium ion mechanism is involved, for this would require the formation of primary carbonium ions. An alternate possibility is that the nitrile nucleophilically attacks the oxonium salt (27) of the epoxide to give the nitrilium salts 28 and 29, which then cyclize, thus:



²⁵ P. A. S. Smith and J. M. Sullivan, *J. Org. Chem.* **26**, 1132 (1961).

B. NITRILIUM SALTS

Although the term "nitrilium salt" was used for the first time in 1931,²⁶ the actual existence of these interesting compounds was not established until 1955 as a result of the work of Klages^{27, 28} and Meerwein.^{29, 30} Nevertheless, long before this last date it was common knowledge that non-isolable intermediate nitrilium salts are formed in numerous reactions. This is specifically the case in the Ritter reaction (Section II, A), as well as in many cognate reactions between nitriles and alkyl halides,³¹ isoparaffins,³² or α -trisubstituted acids,³³ all of which yield a carbonium ion in the presence of sulfuric acid.



The same is also true for certain reactions taking place between nitriles and cyclohexene, in the presence of aluminum chloride and hydrochloric acid,³⁴ which lead to *N*-acyl-cyclohexylamines (**30**), and for similar reactions carried out by Wieland *et al.*,^{35, 36} Cairns *et al.*,³⁷

²⁶ A. Hantzsch, *Ber.* **64**, 667 (1931).

²⁷ F. Klages and W. Grill, *Ann.* **594**, 21 (1955).

²⁸ F. Klages, R. Ruhnau, and W. Hauser, *Ann.* **626**, 60 (1959).

²⁹ H. Meerwein, *Angew. Chem.* **67**, 379 (1955).

³⁰ H. Meerwein, P. Lasch, R. Mersch, and J. Spille, *Ber.* **89**, 209 (1956).

³¹ H. Stetter, J. Mayer, M. Schwarz, and Q. Wulft, *Ber.* **93**, 226 (1960).

³² W. Haaf, *Angew. Chem.* **73**, 144 (1961).

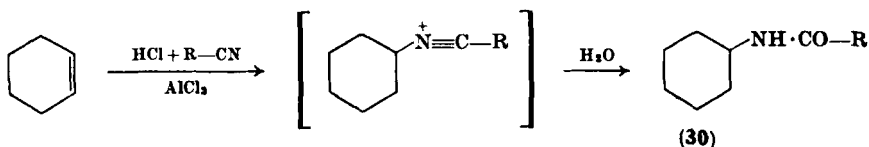
³³ W. Haaf, *Ber.* **96**, 3359 (1963).

³⁴ G. W. Cannon, K. K. Grebber, and Y. K. Hsu, *J. Org. Chem.* **18**, 516 (1953).

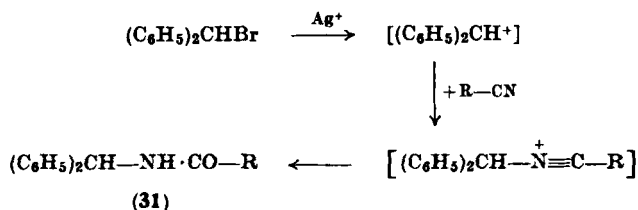
³⁵ H. Wieland and E. Dorrer, *Ber.* **63**, 404 (1930).

³⁶ H. Wieland and C. Hasegawa, *Ber.* **64**, 2516 (1931).

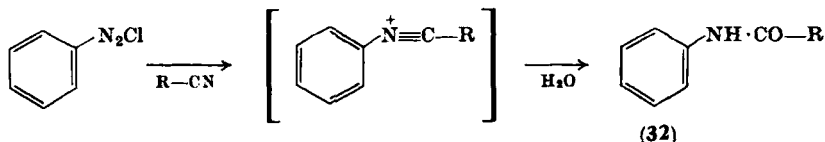
³⁷ T. L. Cairns, P. J. Graham, P. L. Barrick, and R. S. Schreiber, *J. Org. Chem.* **17**, 751 (1952).



and Hamamota and Yoshioka.³⁸ The formation of amides (31) from diphenylmethyl bromide and nitriles in the presence of silver sulfate,³⁹



and that of anilides (32) by decomposition of diazonium salts in the



presence of nitriles,^{40,41} also takes place through an intermediate nitrilium salt.

The participation of nitrilium salts has also been postulated⁴² in the Schmidt reaction and in some Beckmann rearrangements when concentrated sulfuric acid is employed. Hill⁴³ has demonstrated recently that some Beckmann rearrangements carried out in a concentrated sulfuric acid medium are Ritter-type reactions in which the nitrile formed *in situ* from the oxime combines with a carbonium ion to yield a nitrilium salt, which, when diluted with water, leads to the *N*-alkylamide.

³⁸ K. Hamamota and M. Yoshioka, *Nippon Kagaku Zasshi* **80**, 326 (1959); *Chem. Zentr.* **1960**, 3836.

³⁹ J. Cast and T. S. Stevens, *J. Chem. Soc.* **1953**, 4180.

⁴⁰ W. E. Hanby and W. A. Waters, *J. Chem. Soc.* **1939**, 1792.

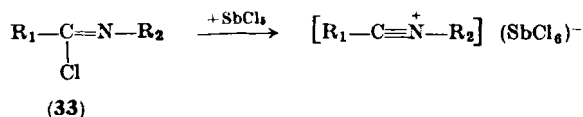
⁴¹ L. G. Makarova and A. N. Nesmeyanov, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk* **1954**, 1019; *Chem. Abstr.* **50**, 241 (1956).

⁴² P. A. S. Smith, *J. Am. Chem. Soc.* **70**, 320 (1948); A. W. Chapman and C. C. Hovis, *J. Chem. Soc.* **1933**, 806; A. W. Chapman, *J. Chem. Soc.* **1934**, 1550.

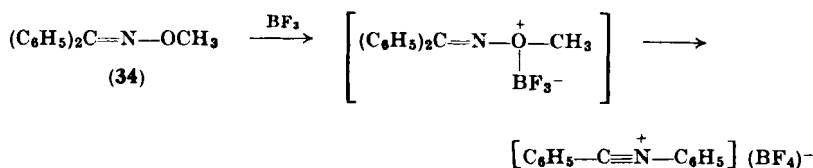
⁴³ R. K. Hill and O. To. Chortyk, *J. Am. Chem. Soc.* **84**, 1064 (1962).

However, the nitrilium salt is not isolated in any of these cases. In 1955, Klages²⁷ and Meerwein²⁹ described, almost simultaneously, the first relatively stable nitrilium salts, and in the course of later work developed general methods for their preparation. These are as follows:

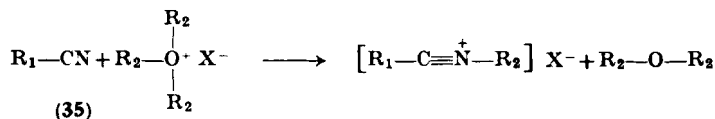
- (a) Treatment of *N*-aryl-substituted iminochlorides (33)^{27, 30} or nitrile-hydrochloric acid addition products²⁸ with electrophilic metal halides, such as SnCl₄, SbCl₅, BF₃, etc.



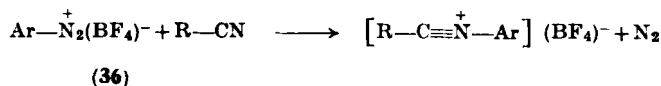
- (b) Reaction between benzophenone oxime, or its methyl ether (34), and boron trifluoride.²⁹



- (c) Alkylation of nitriles by treatment with trialkyloxonium salts (35).³⁰



- (d) Thermal decomposition of diazonium salts (36) in the presence of nitriles.³⁰



- (e) Treatment of nitrile-electrophilic metal halide complexes (37) with simple alkyl halides.³⁰



In every case the isolable compounds obtained have high melting points, in agreement with the saline character assigned to them, are

electrical conductors when dissolved in liquid sulfur dioxide, and show infrared spectra⁴⁴ similar to those of their correspondingly substituted acetylene isosteres.

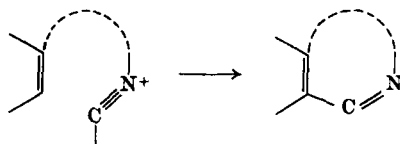
Nitrilium salts show a high reactivity, which has been put to good use in carrying out diverse heterocyclizations. In this section the most prominent examples investigated up to April 1964 are reviewed.

1. Syntheses Involving Electrophilic Attack on an Aromatic Nucleus

In nitrilium salts the resonance between the forms **38** and **39** activates the carbon atom toward attack by centers of high electron density. This electrophilic reactivity permits intramolecular cycliza-

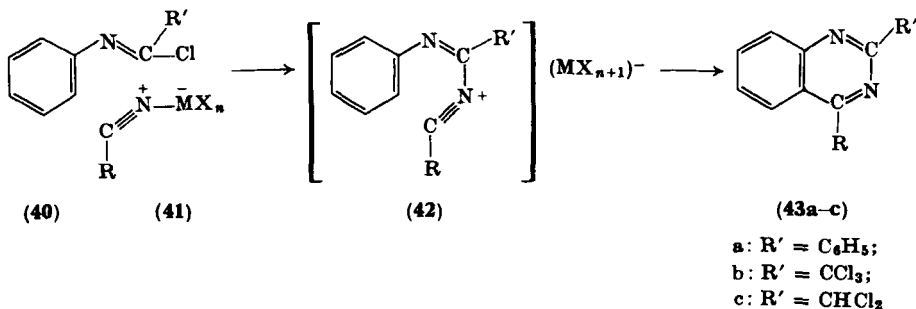


tions, which take place according to Scheme 1, which has been applied to the synthesis of quinazoline, 3,4-dihydroisoquinoline, and 6,7-dihydrothieno[3,2-*c*]pyridine derivatives.



SCHEME 1

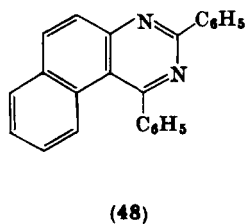
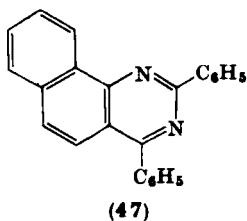
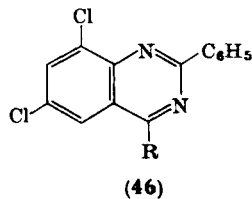
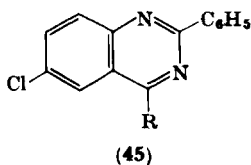
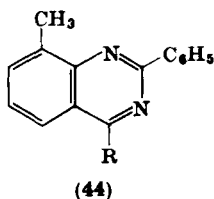
a. *Quinazolines*. Meerwein *et al.*⁴⁵ used the electrophilic activity of nitrilium salts to develop a new method for the synthesis of quinazolines. Nitrilium salts (**42**), obtained by reaction between imino-chlorides (**40**) and nitrile-electrophilic metal halide complexes (**41**),



⁴⁴ J. E. Gordon and G. C. Turnell, *J. Org. Chem.* **24**, 269 (1959).

⁴⁵ H. Meerwein, P. Laasch, R. Mersch, and J. Nentwig, *Ber.* **89**, 224 (1956).

are cyclized under the conditions necessary for their formation, leading to quinazolines (43), generally in good yields (cf. Table IV). This reaction has found application in the preparation of some benzo-

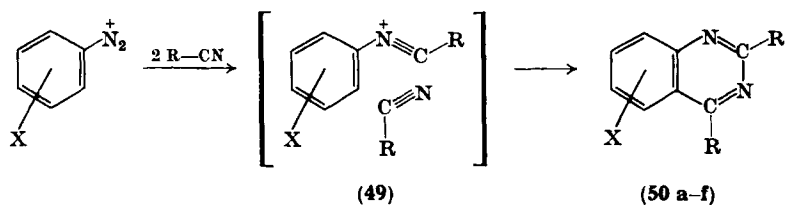


substituted quinazolines (44–46) and condensed systems (47, 48). It can be carried out with *in situ* formation of the iminochloride by treating an amide with thionyl chloride. A slight variation of this method⁴⁵ permits the use of the corresponding iminoether for the iminochloride.

TABLE IV
REPORTED YIELDS (%) OF QUINAZOLINE DERIVATIVES OBTAINED
THROUGH NITRILIUM SALTS⁴⁵

| R | Formulas | | | | | | | | | | | |
|---|----------|-----|-----|----|----|----|-----|-----|-----|-----|-----|-----|
| | 43a | 43b | 43c | 44 | 45 | 46 | 50a | 50b | 50c | 50d | 50e | 50f |
| CH ₃ | 62 | 71 | — | — | — | — | — | — | — | — | — | — |
| C ₂ H ₅ | 88 | — | — | — | — | — | — | — | — | — | — | — |
| CCl ₃ | 33 | 19 | — | — | — | — | — | — | — | — | — | — |
| CH(C ₆ H ₅) ₂ | 94 | — | — | — | — | — | — | — | — | — | — | — |
| C ₆ H ₅ ·CH ₂ | — | — | — | 74 | 83 | 76 | — | — | — | 42 | — | — |
| C ₆ H ₅ | 96 | 78 | 74 | 97 | — | 94 | 58 | 69 | 78 | — | 57 | 22 |
| o-Cl·C ₆ H ₄ | 91 | 62 | 52 | — | — | — | — | — | — | — | — | — |
| COOH | 52 | — | — | — | — | — | — | — | — | — | — | — |
| Br | 86 | — | — | — | — | — | — | — | — | — | — | — |
| N(C ₆ H ₅) ₂ | 96 | — | — | — | — | — | — | — | — | — | — | — |
| S·CH ₃ | 98 | 90 | — | — | — | — | 47 | 49 | — | — | — | — |

Quinazoline derivatives may also be obtained by heating complex diazonium salts with nitriles⁴⁵; under these conditions the nitrilium salt (49) first formed accepts a second nitrile molecule and the resulting product is cyclized by electrophilic attack on the *ortho* position of the

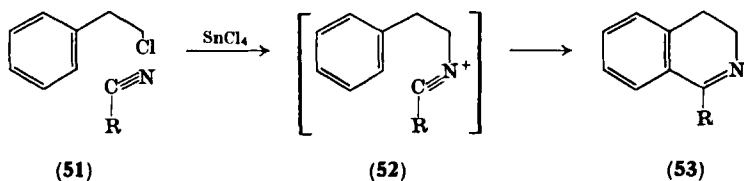


a: X = H; b: X = 6-CH₃; c: X = 6-Cl; d: X = 5,8-(CH₃)₂;

e: X = 5,7-(CH₃)₂; f: X = 5,6- or 6,7-(CH₃)₂

aromatic nucleus. Yields are fairly good, although lower than those obtained by the method mentioned above (cf. Table IV).

b. *3,4-Dihydroisoquinolines*. The 3,4-dihydroisoquinoline synthesis developed by Lora-Tamayo *et al.*^{46, 47} employs β -halogenoalkylbenzene derivatives (51) as halogen components. The nitrilium salts (52) so obtained cyclize spontaneously, yielding 3,4-dihydroisoquinoline derivatives (53). This reaction has been successfully

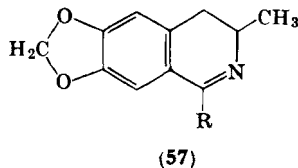
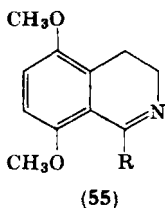
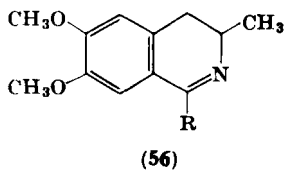
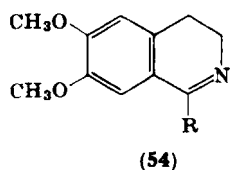


employed in the preparation of 3,4-dihydropapaverine and related compounds (54-57).⁴⁸ Although generally good (cf. Table V), yields are dependent on the nature of the nitrile and halogen component employed, by the influence that their substituents exert on: (a) formation of the nitrile-metal halide complex; (b) formation of the nitrilium salt; and (c) cyclization of the latter.

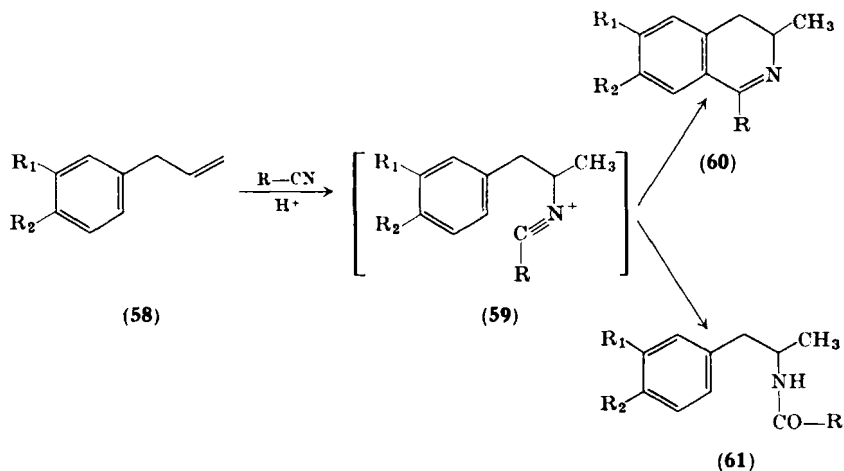
⁴⁶ M. Lora-Tamayo, R. Madroñero, and G. García Muñoz, *Chem. Ind. (London)* **1959**, 657.

⁴⁷ M. Lora-Tamayo, R. Madroñero, and G. García Muñoz, *Ber.* **93**, 289 (1960).

⁴⁸ M. Lora-Tamayo, R. Madroñero, G. García Muñoz, J. Martínez Marzal, and M. Stud, *Ber.* **94**, 199 (1961).



Agbalyan *et al.*⁴⁹ recently employed this reaction in the synthesis of several 3,4-dihydroisoquinoline derivatives with unsaturated substituents in the 1-position. The Madrid group⁵⁰ has shown that (with the exception of benzyl thiocyanate) aliphatic and aromatic thiocyanates yield 1-alkylthio- and 1-arylthio-3,4-dihydroisoquinolines as expected (cf. Table V).



⁴⁹ S. G. Agbalyan, A. O. Nshanyan, and L. A. Nersesyan, *Izv. Akad. Nauk Arm. SSR, Khim. Nauki* **15**, 399 (1962).

⁵⁰ M. Lora-Tamayo, R. Madroñero and D. Gracián, Unpublished work (1963).

TABLE V
REPORTED YIELDS (%) OF 3,4-DIHYDROISOQUINOLINE DERIVATIVES
OBTAINED FROM β -HALOGENOALKYL BENZENES AND TIN
TETRACHLORIDE-NITRILE COMPLEXES

| R | Formulas | | | | |
|---|--------------------|-----------------|--------------------|-----------------|-----------------|
| | 53 ^a | 54 ^b | 55 ^b | 56 ^b | 57 ^b |
| H | 14 | — | — | — | — |
| CH ₃ | 91 | 58 | 82 | 91 | 75 |
| C ₂ H ₅ | 100 | — | 65 | 92 | 63 |
| <i>n</i> -C ₃ H ₇ | — | — | 60 | — | — |
| <i>i</i> -C ₃ H ₇ | — | 100 | — | — | — |
| CCl ₃ | 0 | — | — | — | — |
| CH ₃ OCH ₂ | — | — | 51 | 60 | 64 |
| CH ₂ =CH | 12 ^c | — | — | — | — |
| CH ₂ =CH—CH ₂ | 13 ^c | — | — | — | — |
| CCl ₂ =CH—(CH ₂) ₃ | 5 ^c | — | — | — | — |
| C ₆ H ₅ ·CH ₂ | 55 | 80 | 55 ^d | 64 | 79 |
| <i>p</i> -CH ₃ O·C ₆ H ₄ ·CH ₂ | 6 | — | — | — | — |
| 3,4-(CH ₃ O) ₂ C ₆ H ₃ ·CH ₂ | — | 21 | — | 30 | 23 |
| <i>p</i> -Cl·C ₆ H ₄ ·CH ₂ | — | — | 54 | — | — |
| C ₆ H ₅ | 65 | 82 | 83 | 69 | 53 |
| <i>p</i> -CH ₃ ·C ₆ H ₄ | 59 | — | — | — | — |
| <i>p</i> -CH ₃ O·C ₆ H ₄ | 8 | — | 37 | 32 | 30 |
| 3,4-(CH ₃ O) ₂ C ₆ H ₃ | 10 | — | 30 | 17 | 52 |
| 3,4-(CH ₂ O) ₂ C ₆ H ₃ | — | — | — | 12 | 45 |
| <i>o</i> -NO ₂ ·C ₆ H ₄ | 50 | — | — | 6 | — |
| <i>m</i> -NO ₂ ·C ₆ H ₄ | 48 | — | 50 | 50 | — |
| <i>p</i> -NO ₂ ·C ₆ H ₄ | 23 | — | — | — | — |
| 1-C ₁₀ H ₇ | 26 | — | — | — | — |
| 2-C ₁₀ H ₇ | 55 | — | — | — | — |
| Alkyl-S | 50–80 ^e | — | 70–80 ^e | — | — |
| Aryl-S | 40–60 ^e | — | — | — | — |

^a Lora-Tamayo *et al.*⁴⁷ where not otherwise indicated.

^b Lora-Tamayo *et al.*⁴⁸ where not otherwise indicated.

^c Agbalyan *et al.*⁴⁹

^d In an inert atmosphere, 80% yield, according to Lora-Tamayo.⁴⁷

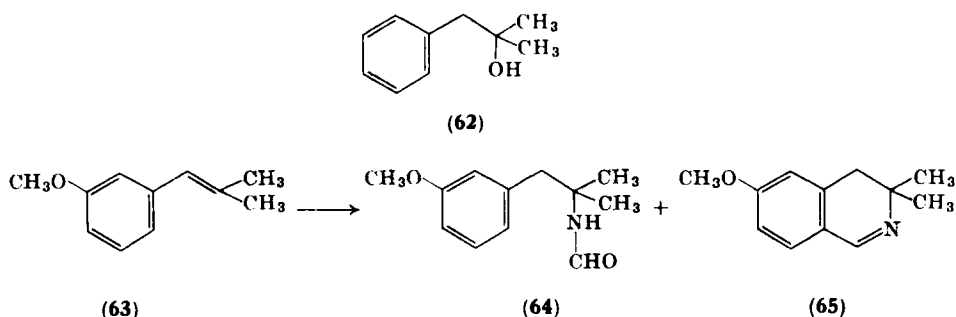
^e Lora-Tamayo *et al.*⁵⁰

We must here draw attention to several reactions taking place between propenylbenzenes (58) and nitriles in the presence of concentrated sulfuric acid,^{24, 51} for they also may take place through an

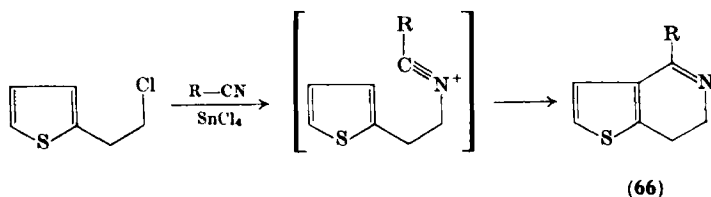
⁵¹ J. J. Ritter and J. Kalish, *J. Am. Chem. Soc.* **70**, 4048 (1948).

intermediate nitrilium salt (59). With the sole exception of methyleugenol (58, $R_1 = R_2 = \text{OCH}_3$), the propenylbenzenes studied either do not react under these conditions or yield amides (61) as a result of nitrilium salt hydrolysis. In three instances only was the nitrilium salt (59) (from methyleugenol and 4-methoxy-, 3,4-dimethoxy-, or 3,4-diethoxy-benzonitrile) found to cyclize, to form the corresponding 3,4-dihydroisoquinoline derivative (60), in low yield.

The alcohol (62) also reacts with nitriles to give amides^{24, 51} but reaction of the olefin (63) with hydrocyanic and sulfuric acids⁵² yields an amide (64)-3,4-dihydroisoquinoline (65) mixture.



c. *6,7-Dihydro-thieno[3,2-c]pyridines*. The method employed in the synthesis of 3,4-dihydroisoquinoline derivatives (Section II, B, 1, b) has been extended⁵³ to other non-benzenoid aromatic halogen components, such as 2-(β -chloroethyl)-thiophene. However, the yields



(cf. Table VI) are considerably lower. Neither 2-(β -chloroethyl)-furan nor 2-(β -chloroisopropyl)-pyridine reacts with nitrile-stannic chloride complexes under similar conditions.

⁵² H. Wollweber and R. Hittmann, *Angew. Chem.* **72**, 1001 (1960).

⁵³ M. Lora-Tamayo, R. Madroñero and M. G. Pérez, *Ber.* **95**, 2188 (1962).

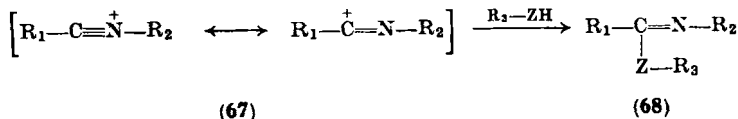
TABLE VI

REPORTED YIELDS OF 6,7-DIHYDRO-THIENO[3,2-*c*]PYRIDINES OBTAINED FROM 2-(β -CHLOROETHYL)-THIOPHENE AND TIN TETRACHLORIDE-NITRILE COMPLEXES⁵³

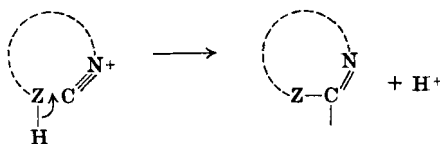
| R in formula 66 | Yield (%) | R in formula 66 | Yield (%) |
|--|-----------|---|-----------|
| CH ₃ | 17 | C ₆ H ₅ ·CH ₂ | 15 |
| C ₂ H ₅ | 12 | (C ₆ H ₅) ₂ CH | 0 |
| <i>n</i> -C ₃ H ₇ | 16 | C ₆ H ₅ | 13 |
| iso-C ₃ H ₇ | 16 | <i>p</i> -CH ₃ ·C ₆ H ₄ | 9 |
| CH ₃ O·CH ₂ ·CH ₂ | 17 | <i>p</i> -CH ₃ O·C ₆ H ₄ | 8 |

2. Syntheses Involving Reactions with Electron-Rich Groups

Another aspect of the reactivity of nitrilium salts has been employed in the synthesis of several heterocyclic systems. This entails their reaction with certain electron-rich functional groups, such as —OH, —SH, —NH₂, etc.,^{27,30} according to the general scheme (67 → 68) yielding iminoethers (68, Z = O), iminothioethers (68, Z = S),



amidines (68, Z = NH), etc., respectively. This has opened the way for heterocyclizations of the type shown in Scheme 2.



SCHEME 2

By using experimental conditions typical for the Ritter reaction, the scheme has been applied to the synthesis of 5,6-dihydro-4*H*-1,3-oxazines^{9, 11-14, 54} and 2-oxazolines¹⁵ (taking advantage of the nitrilium salt reactivity for the —OH grouping); 5,6-dihydro-4*H*-1,3-thiazines^{11, 55} and 2-thiazolines^{17, 55} (exploiting the reactivity

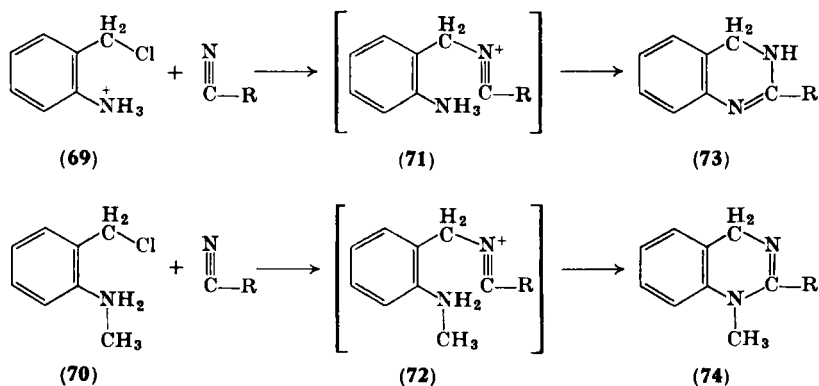
⁵⁴ A. I. Meyers, *J. Org. Chem.* **26**, 218 (1961).

⁵⁵ A. I. Meyers, *J. Org. Chem.* **25**, 1147 (1960).

for the —SH grouping); and 1-pyrrolines^{11, 17} and 5,6-dihydropyridines^{14, 17, 22, 56} (using the reactivity toward the C=C system).

Although Ritter^{9, 17} postulated that the above reactions involve an imidol hydrogen sulfate, Meyers⁵⁵ has expressed the view that a nitrilium salt may be the intermediate, and this is also the present authors' opinion. These reactions are probably no different in kind. Nevertheless, they are not further discussed here since they are reviewed elsewhere in this chapter (Section II, A) and only those aspects of the Ritter reaction which may enable one to draw comparisons with "true" nitrilium salt reactions will be included, as in the previous section.

a. *3,4- and 1,4-Dihydroquinazolines*. The possibility of an amino group participating in intramolecular cyclization reactions with an appropriately located nitrilium salt grouping, according to Scheme 2, has recently been established⁵⁷ in a new synthesis of 3,4- and 1,4-dihydroquinazoline derivatives. In this method *o*-aminobenzyl chloride hydrochloride (69) or its *N*-methyl derivative (70) reacts with nitrile-stannic chloride complexes to yield nitrilium salts (71, 72); under the conditions necessary for their formation, the latter cyclize spontaneously and yield, respectively, 3,4- or 1,4-dihydroquinazolines (73,



⁵⁶ A. I. Meyers, N. K. Ralhan, and G. García Muñoz, in "Congress Lectures, XIX International Congress of Pure and Applied Chemistry, London, 1963," p. 224 (Abstracts). Butterworth, London and Washington, D.C., 1963.

⁵⁷ M. Lora-Tamayo, R. Madroñero and G. García Muñoz, *Ber.* **94**, 208 (1961); G. García Muñoz, M. Lora-Tamayo, R. Madroñero, and J. Martínez Marzal, *Anales Real Soc. Españ. Fis. Quim. (Madrid) Ser. B* **57**, 277 (1961).

74). In both cases,⁵⁸ yields are good and do not appear to be dependent on the nature of the nitrile employed (cf. Table VII).

TABLE VII
REPORTED YIELDS (%) OF 3,4- AND 1,4-DIHYDROQUINAZOLINES OBTAINED
THROUGH NITRILIUM SALTS⁵⁷

| R | Formulas | | R | Formula 73 |
|---|----------|----|---|---------------|
| | 73 | 74 | | |
| CH ₃ | 68 | 85 | CH ₃ O·CH ₂ | 68 |
| C ₂ H ₅ | 92 | — | <i>m</i> -NO ₂ ·C ₆ H ₄ | 96 |
| <i>n</i> -C ₃ H ₇ | 91 | — | C ₆ H ₅ ·CH ₂ | 100 |
| C ₆ H ₅ | 89 | 83 | <i>o</i> -Cl·C ₆ H ₄ ·CH ₂ | 40 |
| <i>p</i> -CH ₃ O·C ₆ H ₄ | 75 | 80 | <i>p</i> -Cl·C ₆ H ₄ ·CH ₂ | 93 |
| <i>o</i> -NO ₂ ·C ₆ H ₄ | 71 | 75 | 1-C ₁₀ H ₇ | 90 |

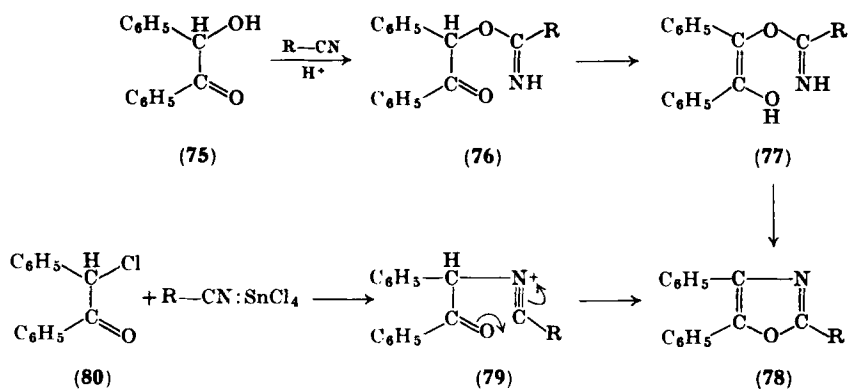
b. *Oxazoles*. The work of Japp and Murray⁵⁹ certainly entails one of the first applications of nitrilium salts in heterocyclic synthesis, despite their misinterpretation of the reaction. In its reactions with nitriles, in the presence of concentrated sulfuric acid, benzoin (75) gives oxazole derivatives (78), probably via an intermediate nitrilium salt (79), although in the above-mentioned paper the reaction scheme (75 → 76 → 77 → 78) is postulated.

Desyl chloride (80) also yields oxazole derivatives (78) when it reacts with several nitrile-stannic chloride complexes,⁶⁰ but other chloroketones studied either do not react (2-chlorocyclohexanone and

⁵⁸ The assertion of W. L. F. Armarego [*in* "Advances in Heterocyclic Chemistry" (A. R. Katritzky, ed.), Vol. 1, pp. 282–283. Academic Press, New York, 1963], "attempts made to prepare 1,2-dimethyl-1,4-dihydroquinazolines from *o*-methylaminobenzyl chloride hydrochloride and acetonitrile in the presence of stannic chloride gave 1,2-dimethyl-4(1*H*)-quinazolinone [M. Lora-Tamayo, R. Madroñero, and G. G. Muñoz, *Ber.* **94**, 208 (1961)]", is mistaken. This type of reaction has permitted the preparation, *for the first time*, not only of 1-methyl-2-phenyl-, 1-methyl-2-(*o*-nitrophenyl)-, and 1-methyl-2-(*p*-methoxyphenyl)-1,4-dihydroquinazolines, but also of 1,2-dimethyl-1,4-dihydroquinazoline. The stability of these compounds depends in a great measure on the substituent on position 2. Contrary to the statement of Armarego, the infrared spectrum of the tin complex has not been recorded by us.

⁵⁹ F. R. Japp and T. S. Murray, *J. Chem. Soc.* **63**, 469 (1893).

⁶⁰ M. Lora-Tamayo, R. Madroñero, and H. Leipprand, *Ber.* **97**, 2230 (1964).



chloroacetone) or, if they do, yield is very small (phenacyl bromide and chloropropiophenone). Doubtless the reaction proceeds via the nitrilium salt (79) and it has opened the way for the preparation of several compounds (cf. Table VIII).

Benzilic acid (81) also reacts with benzonitrile in the presence of sulfuric acid; however, it does not yield 2,5,5-triphenyl-oxazolin-4-one (82) as indicated originally,⁶¹ but the 2,4,4-triphenyl isomer (83).^{62, 63}

TABLE VIII
REPORTED YIELDS (%) OF OXAZOLE DERIVATIVES OBTAINED THROUGH
NITRILIUM SALTS^a

| R in Formula 78 | Yield (%) | R in Formula 78 | Yield (%) |
|--|-----------------|---|-----------------|
| CH ₃ | 75 ^b | C ₆ H ₅ | 92 ^c |
| C ₂ H ₅ | 63 ^d | <i>p</i> -CH ₃ O·C ₆ H ₄ | 76 |
| <i>n</i> -C ₃ H ₇ | 69 | <i>m</i> -NO ₂ ·C ₆ H ₄ | 63 |
| <i>iso</i> -C ₃ H ₇ | 61 | CH ₃ ·S | 65 ^e |
| CH ₃ O·CH ₂ | 52 | C ₂ H ₅ ·S | 85 ^e |
| C ₆ H ₅ ·CH ₂ | 74 | C ₆ H ₅ ·S | 30 ^e |

^a Lora-Tamayo *et al.*⁶⁰ where not otherwise indicated.

^b Crude yield of 40% from benzoin and acetonitrile, in the presence of sulfuric acid, has been reported by Japp and Murray.⁵⁹

^c Unspecified yield from benzoin and benzonitrile in the presence of sulfuric acid.⁵⁹

^d Crude yield of 20% from benzoin and propionitrile in the presence of sulfuric acid.⁵⁹

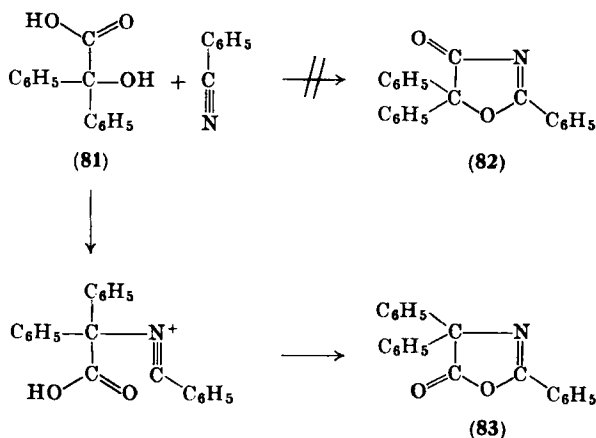
^e Lora-Tamayo *et al.*⁵⁰

⁶¹ F. R. Japp and A. Findley, *Proc. Chem. Soc.* **15**, 165 (1899); *Chem. Zentr.* **II**, 252 (1899); *J. Chem. Soc.* **75**, 1027 (1899).

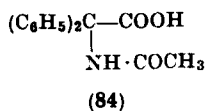
⁶² H. Hohenlohe-Oehringen, *Monatsh.* **93**, 639 (1962).

⁶³ C. W. Bird, *J. Org. Chem.* **27**, 4091 (1962).

No other oxazolinone has apparently been prepared by this method; acetonitrile reacts with benzoic acid⁶⁴ to yield the corresponding



amide (84), which can be cyclized by ordinary methods to yield the oxazolinone. Several unsaturated acids and esters studied by Hartzel and Ritter⁷ show a similar behavior.



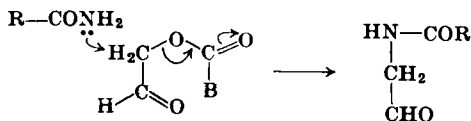
Ferrini and Marxer⁶⁵ have recently shown that vinylene carbonate reacts with primary amides, in the presence of polyphosphoric acid, to yield 2-substituted oxazole derivatives. Yields are low (2–34%), and phenoxy- and phenyl-acetamide, *p*-methylbenzamide, and salicylamide do not give oxazole derivatives. Although the reaction has been interpreted according to Scheme 3, the nucleophilic attack of a nitrile molecule (from the amide dehydration), with a nitrilium salt as intermediate (Scheme 4), cannot be excluded.⁶⁶

c. *4H-1,3-Oxazines*. The use of β -chloroketones (85) as halogen components in nitrilium salt formation has led to the development of

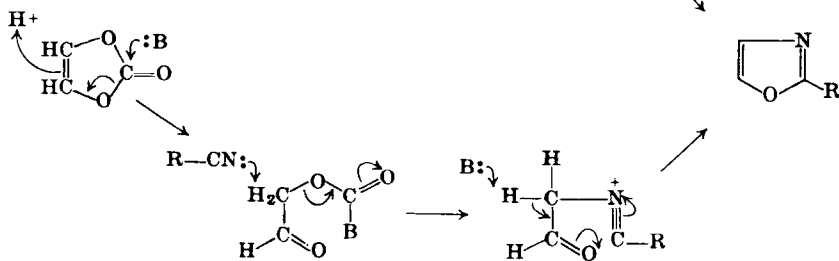
⁶⁴ H. Hohenlohe-Oehringen, *Monatsh.* **93**, 645 (1962).

⁶⁵ P. G. Ferrini and A. Marxer, *Angew. Chem.* **75**, 165 (1963).

⁶⁶ This interpretation, and its extension to ethylene sulfides, trimethylene oxides, thietanes, azetidines, and related compounds is now being tested in the laboratory of the "Alonso Barba" Institute.

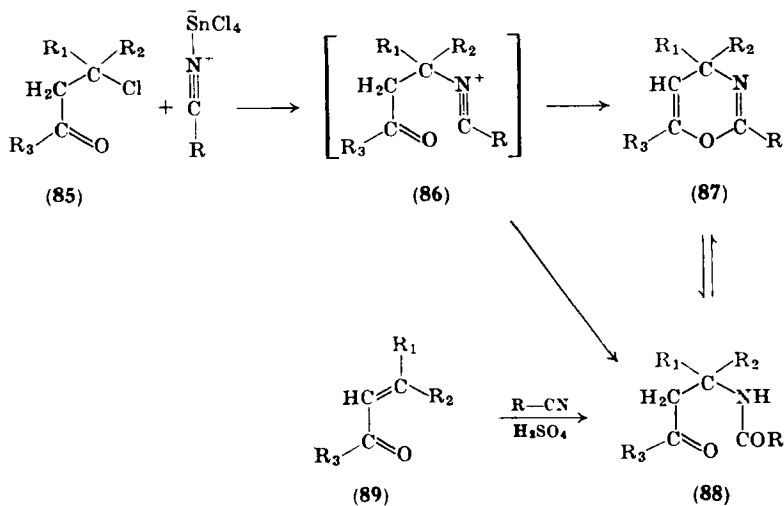


SCHEME 3



SCHEME 4

a new synthetic method for preparing 4*H*-1,3-oxazines,⁶⁷ in which the intermediate nitrilium salt (86), which is formed in the reaction between those chloroketones and several nitrile-stannic chloride



a: $\text{R}_1 = \text{R}_2 = \text{R}_3 = \text{CH}$ b: $\text{R}_1 = \text{R}_3 = \text{C}_6\text{H}_5$, $\text{R}_2 = \text{H}$

⁶⁷ M. Lora-Tamayo, R. Madroñero, G. García Muñoz, and H. Leipprand, *Ber.* **97**, 2234 (1964).

complexes, is cyclized to yield **87**. Although yields obtained (cf. Table IX) depend, in the main, on the relative stability of these compounds in acid media, they are generally good. In every case variable amounts of the corresponding amido-ketone (**88**) are isolated. The formation of this compound is attributed to the hydrolysis of the 4*H*-1,3-oxazine under conditions required for its isolation as well as to the hydrolysis of the nitrilium salt (**86**) before cyclization takes place.⁶⁸

TABLE IX
REPORTED YIELDS (%) OF 4*H*-1,3-OXAZINE DERIVATIVES
(**87**) AND ACYLAMINOKETONES (**88**) OBTAINED THROUGH
NITRILIUM SALTS^a

| R | Formulas | | | |
|---|------------|------------|------------|------------|
| | 87a | 88a | 87b | 88b |
| CH ₃ | 31 | 47 | 0 | 71 |
| C ₂ H ₅ | 26 | 45 | — | — |
| <i>n</i> -C ₃ H ₇ | 40 | 30 | 0 | 90 |
| iso-C ₃ H ₇ | 25 | 37 | — | — |
| <i>n</i> -C ₁₇ H ₃₅ | 0 | 80 | — | — |
| CH ₃ O·CH ₂ | 28 | 50 | — | — |
| CH ₃ O·CH ₂ CH ₂ | 22 | 55 | — | — |
| NC·CH ₂ ·CH ₂ | 5 | 0 | — | — |
| ClCH ₂ | 0 | 77 | — | — |
| ClCH ₂ ·CH ₂ | 0 | 63 | — | — |
| C ₆ H ₅ ·CH ₂ | 45 | 20 | 0 | 70 |
| (C ₆ H ₅) ₂ CH | 0 | 6 | — | — |
| C ₆ H ₅ | 57 | 15 | 0 | 62 |
| <i>p</i> -CH ₃ ·C ₆ H ₄ | 50 | 15 | 70 | 0 |
| <i>p</i> -CH ₃ O·C ₆ H ₄ | 60 | 0 | — | — |
| <i>p</i> -Cl·C ₆ H ₄ | 0 | 61 | — | — |
| <i>o</i> -NO ₂ ·C ₆ H ₄ | 5 | 0 | — | — |
| CH ₃ S ^b | 45 | 35 | — | — |
| C ₂ H ₅ S ^b | 40 | 32 | — | — |

^a Lora-Tamayo *et al.*⁶⁷ where not otherwise indicated.

^b Lora-Tamayo *et al.*⁵⁰

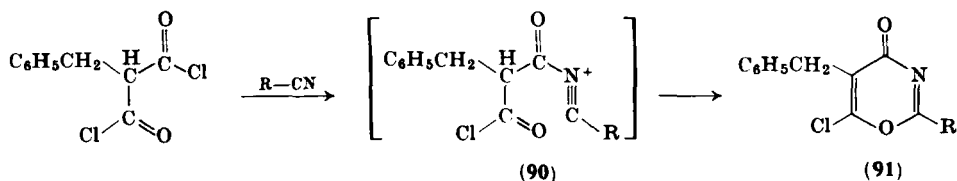
The reaction has also been successfully applied to the preparation of some 4,4,6-trimethyl-2-alkylthio-4*H*-1,3-oxazines.⁶⁹

⁶⁸ M. Lora-Tamayo, R. Madroñero and H. Leipprand, *Ber.* **97**, 2244 (1964).

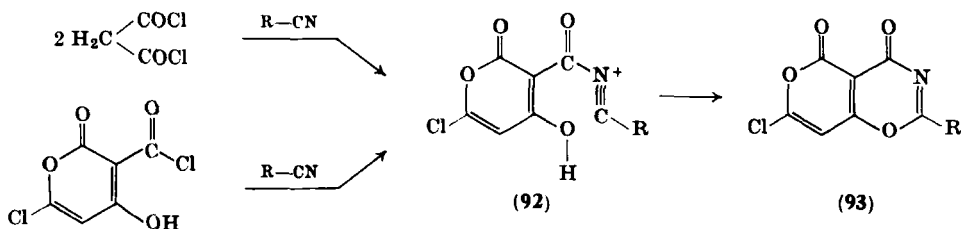
⁶⁹ M. Lora-Tamayo, R. Madroñero and V. Gómez, Unpublished work (1963).

It should be mentioned that Ritter⁷⁰ writes about the application of his reaction to mesityl oxide, although he omits details of the resulting products. Schener *et al.*⁷¹ have drawn attention to the fact that mesityl oxide (**89a**) reacts with benzonitrile in the presence of sulfuric acid to yield the amide (**88a**, $R = \text{CH}_3$) (20%). In neither case is the formation of a 4*H*-1,3-oxazine mentioned. Chalcone (**89b**) does not react⁷¹ with benzonitrile; however, it does react with acetonitrile to yield a small amount of 3-acetamido-3-phenylpropio-phenone and a substance, the structure of which is still to be established. The structure 2-(1'-acetamido-2'-benzoyl)-ethyl-benzenesulfonic acid sultam has been postulated for it, although the possibility of its being a 2-methyl-4,6-diphenyl-4*H*-1,3-oxazine with a sulfonic group in one of its two aromatic rings is not entirely ruled out.

We should also mention that Ziegler *et al.*⁷² have described the formation of 1,3-oxazine-4-ones (**91**) by reactions taking place between benzylmalonyl chloride and several nitriles. They interpret the process as taking place via an *N*-acyl-nitrilium salt (**90**).



A similar procedure, taking advantage of the nitrilium salt reactivity for the $-\text{OH}$ grouping, permits the synthesis of several 5-oxo-pyrano[3,4-*e*]-1,3-oxazine derivatives (**93**) which Davis and Elvidge⁷³ have recently described and in the formation of which an intermediate *N*-acyl-nitrilium salt (**92**) has also been postulated.



⁷⁰ J. J. Ritter, U.S. Patent 2,573,673 (1951); *Chem. Abstr.* **46**, 9584 (1952).

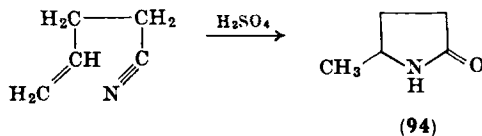
⁷¹ P. J. Schener, H. C. Botelho, and C. Pauling, *J. Org. Chem.* **22**, 674 (1957).

⁷² E. Ziegler, G. Kleineberg, and H. Meindl, *Monatsh.* **94**, 544 (1963).

⁷³ S. J. Davis and J. A. Elvidge, *J. Chem. Soc.* 3553 (1962).

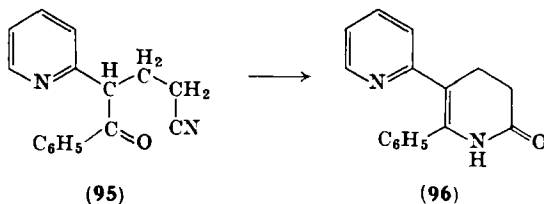
C. MISCELLANEOUS REACTIONS

Schnell and Nentwig⁷⁴ mention that 5-methylpyrrolidin-2-one (**94**) has been obtained from 4-cyanobut-1-ene by using typical Ritter experimental conditions.

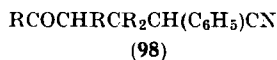
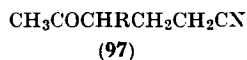


Little attention seems to have been paid to this type of reaction involving intramolecular nitrilium salt formation. Typical experimental conditions of the Ritter reaction have always been employed in the few instances which have been studied. The reaction does not appear to be widely applicable and at least three exceptions have been recorded in the literature.⁷⁵⁻⁷⁷

The cyclization of δ -ketonitriles by anhydrous acids⁷⁸ has received some attention in recent years. Beyer and Leverenz⁷⁹ observed that hydrogen bromide in chloroform converts **95** into **96** in good yield.



Similar cyclizations of **97** and **98**, using hydrogen chloride⁸⁰ and concentrated sulfuric acid,⁸¹ respectively, have also been recorded.



⁷⁴ H. Schnell and J. Nentwig, in "Methoden der organischen Chemie" (J. Houben and T. Weyl, eds.) Vol. 11, Part 2, p. 561. Thieme, Stuttgart, Germany, 1958.

⁷⁵ F. H. Howell and D. A. H. Taylor, *J. Chem. Soc.* **1957**, 3011.

⁷⁶ R. T. Conley and B. E. Nowak, *J. Org. Chem.* **27**, 1965 (1962).

⁷⁷ R. T. Conley and M. C. Annis, *J. Org. Chem.* **27**, 1961 (1962).

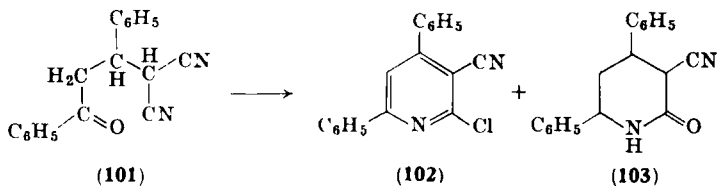
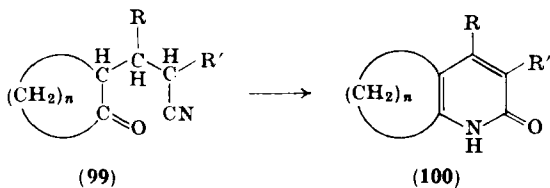
⁷⁸ F. Brody and P. R. Ruby, in "Pyridine and Its Derivatives" (E. Klingsberg, ed.), Vol. I, Chapter 2, p. 288. Wiley (Interscience), New York, 1960.

⁷⁹ H. Beyer and K. Leverenz, *Ber.* **94**, 407 (1960).

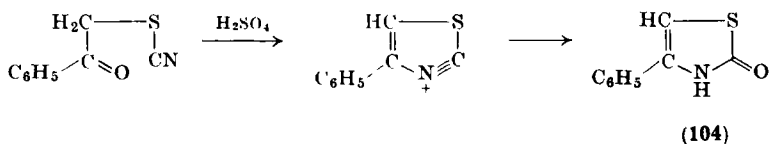
⁸⁰ N. P. Shuskerina, A. V. Golovin, and R. Y. Levina, *Zh. Obshch. Khim.* **30**, 1762 (1960).

⁸¹ A. Vigier and J. Dreux, *Bull. Soc. Chim. France* **10**, 2294 (1963).

Most recently Meyers and García Muñoz⁸² have demonstrated that ketonitriles of structure **99** undergo both cyclization and dehydrogenation to the pyridones (**100**) when treated with 96% sulfuric acid. They consider the cyclization reaction to be a further extension of the



Ritter reaction. A similar cyclization dehydrogenation reaction had previously been observed by Kohler and Souther,⁸³ who obtained both **102** and **103** when **101** was treated with dry hydrogen chloride. They suggested that **102** and **103** arose by a disproportionation of the intermediate dihydropyridine.



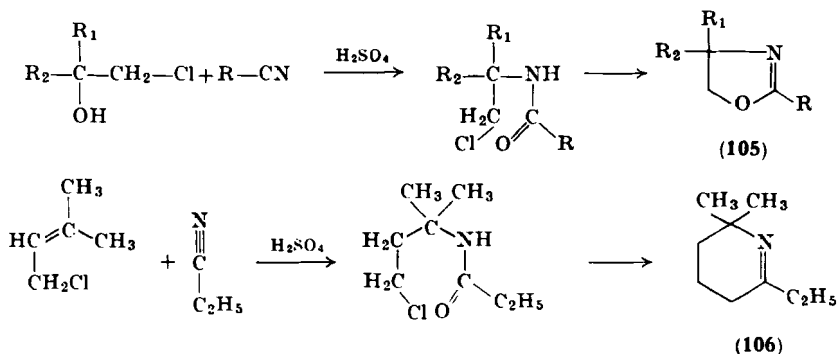
The formation of 5-phenylthiazolin-2-one (**104**), from phenacyl thiocyanate in the presence of concentrated sulfuric acid,⁸⁴ undoubtedly follows a similar pathway (without the dehydrogenation step).

⁸² A. I. Meyers and G. García Muñoz, *Abstr. Papers 147th Meeting Am. Chem. Soc.* 54N (1964).

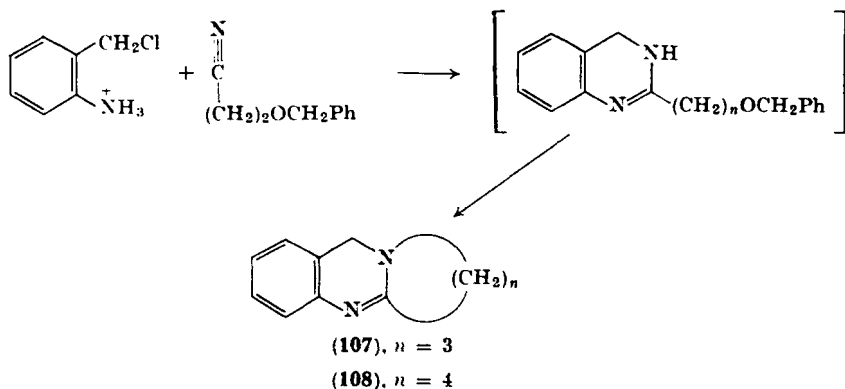
⁸³ E. P. Kohler and B. L. Souther, *J. Am. Chem. Soc.* **44**, 2903 (1922).

⁸⁴ R. Reimschneider and G. Orlick, *Monatsh.* **84**, 311 (1953).

The use of haloalkenes or halohydrins in Ritter-type reactions has resulted in the development of an oxazoline (105) synthesis⁸⁵; yields are 60–70%. The formation of 2-ethyl-4,4-dimethyl-5,6-dihydro-4*H*-1,3-oxazine (106)⁵⁵ from 1-chloro-3-methyl-2-butene and propionitrile in the presence of sulfuric acid has a similar basis.



The use of 4-benzyloxy-butyronitrile and 5-benzyloxy-valeronitrile in the previously mentioned synthesis of 3,4-dihydroquinazoline derivatives (cf. Section II.B.2.a) results in the formation of compounds 107 and 108, respectively.⁸⁶



An interesting new reaction leading to triazines has also been reported.⁸⁷ This involves the action of hydrogen chloride on a hot

⁸⁵ R. M. Lusskin and J. J. Ritter, *J. Am. Chem. Soc.* **72**, 5577 (1950).

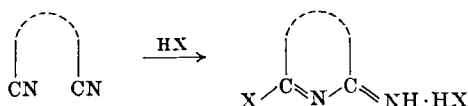
⁸⁶ G. García Muñoz and R. Madroñero, *Ber.* **95**, 2182 (1962).

⁸⁷ H. Weidinger and J. Kranz, *Ber.* **96**, 2070 (1963).

starting from mesityl oxide. This is a very interesting extension of the Ritter reaction, based on the ease with which isoxazole derivatives are hydrolyzed.

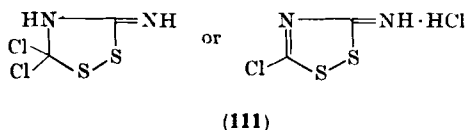
III. Ring Formation Involving Cyclization of an α,ω -Dinitrile

The cyclization reactions of α,ω -dinitriles under the influence of anhydrous hydrogen halides (Eq. 3) at 0–25° have proved to be of considerable synthetic value. A range of aromatic heterocyclic systems becomes available, since it is possible for the *exo*-imine double



bond to migrate into the ring. Their exact nature depends on the inter-nitrile chain. An important consideration is that such systems, wherein the ring nitrogen atom is flanked by halogen and amino functions, were previously either difficultly accessible or unavailable. Even more interesting is the fact that, in the majority of cases, hydrogen chloride does not effect conversion of the dinitriles to the halo-bisimine structure. Previous studies of the action of acids on dinitriles have essentially been confined to the use of the popular hydrochloric and sulfuric acids, and this probably accounts for the fact that the generality of the reaction was not discovered at least 50 years ago. Its simplicity makes it something of an anachronism. With the latter acids, the products are imides^{88a} if the expected ring has little strain; otherwise bisamides are produced. The reaction (Eq. 3) is closely related to imide formation and also has kinship with the acid-catalyzed trimerization of nitriles to triazines.

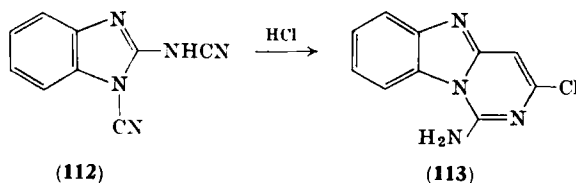
A few early references ascribe cyclic structures to the action of hydrogen halides on α,ω -dinitriles. Söderback⁸⁹ assigned structure



^{88a} F. Brody and P. R. Ruby in "Pyridine and Its Derivatives" (E. Klingsberg, ed.), Vol. I, Chapter 2, p. 298. Wiley (Interscience), New York, 1960.

⁸⁹ A. Söderback, *Ann.* **419**, 217 (1919).

111 to the product from thiocyanogen and hydrogen chloride, and Pellizzari⁹⁰ obtained **113** by the action of concentrated hydrochloric acid on **112**. Most of the research activity in the area, however, has occurred in recent years.

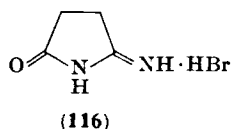
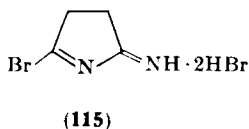
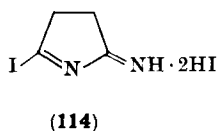


A. NON-AROMATIC RING SYSTEMS

Only a limited number of dinitriles which would lead to non-aromatic systems on cyclization have been studied thus far.

1. 1-Pyrrolines and Tetrahydropyridines

Biltz⁹¹ first examined the action of concentrated hydriodic acid on succinonitrile and obtained a product which was claimed to contain four equivalents of hydrogen iodide. The analytical data, however, agree better with the empirical formula $\text{C}_4\text{H}_4\text{N}_2 \cdot 3\text{HI}$, and undoubtedly this material has the structure **114** in accordance with the recent work of Howard,⁹² Osborn,⁹³ and Johnson.⁹⁴ These investigators found that hydrogen bromide causes an immediate precipitation of **115** from a solution of succinonitrile in ether, benzene, or acetic



acid. The proof of structure of **115** lies in its conversion to **116** on treatment with water or alcohol and its further hydrolysis to succinimide. So far, attempts to isolate the free base of **115** have not succeeded,⁹⁴ due to the very high reactivity of the bromine atom.

⁹⁰ G. Pellizzari, *Gazz. Chim. Ital.* **52 I**, 199 (1922); **54 I**, 177 (1924).

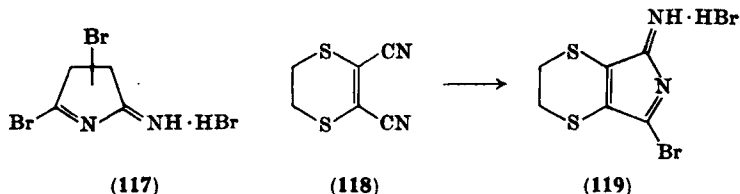
⁹¹ H. Biltz, *Ber.* **25**, 2543 (1892).

⁹² E. G. Howard, Jr., U.S. Patent 2,810,726 (1957).

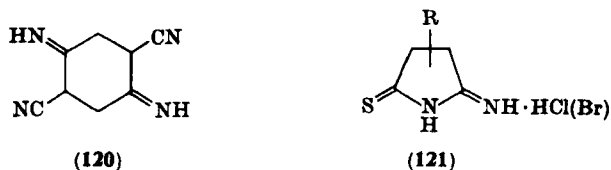
⁹³ J. H. Osborn, Ph.D. Thesis, University of Minnesota (1958); *Diss. Abstr.* **1959**, 2475.

⁹⁴ F. Johnson, Unpublished results (1959).

Substituted succinonitriles behave similarly, giving the corresponding 2-bromo-^{92, 93} or 2-iodo-5-imino-1-pyrroline^{94, 95} hydrohalides. Where the substitution is unsymmetrical, the products must be regarded as mixtures, since substituents do not appear to affect the direction of cyclization. Fumaronitrile affords **117** when treated with hydrogen bromide,⁹² and the structure of the salt obtained⁹⁶ by the action of hydrogen bromide on **118** is probably **119**.



The reaction of hydrogen chloride with succinonitrile does not lead to the expected pyrroline but takes a different course and affords **120** as the product.⁹⁷



Nevertheless, if the cyclization of the succinonitrile with this acid is carried out in the presence of thiolacetic acid, 2-imino-5-thioxo-pyrrolidine hydrohalides (**121**) are obtained in good yield.⁹⁸ These compounds very readily convert benzaldehyde to thiobenzaldehyde trimer.

The reactions of glutaronitriles parallel very closely those described above for succinonitriles. Glutaronitrile itself, for example, reacts with hydrogen bromide or iodide, affording 6-bromo-2,3,4,5-tetrahydro-2-iminopyridine dihydrobromide,^{92, 93} (**122**) or the corresponding iodo-dihydroiodide.⁹⁴ These compounds on neutralization with cold sodium hydroxide do afford the free bases⁹² so that the ring halogen atoms are not as labile as in the case of the pyrrolines (**115**). Again,

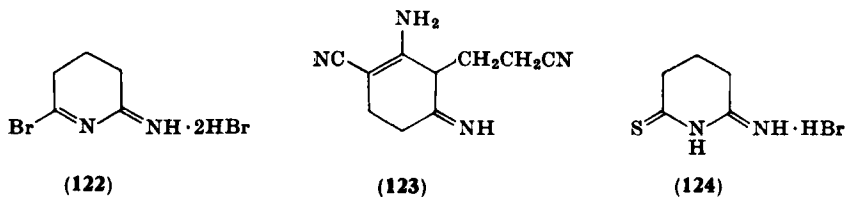
⁹⁵ N. O. Brace, *J. Org. Chem.* **28**, 3093 (1963).

⁹⁶ W. Wolf, D. Degener, and S. Petersen, *Angew. Chem.* **72**, 963 (1960).

⁹⁷ J. Decombe and C. Verry, *Compt. Rend.* **256**, 5156 (1963).

⁹⁸ E. G. Howard, Jr., U.S. Patent 2,841,588 (1958).

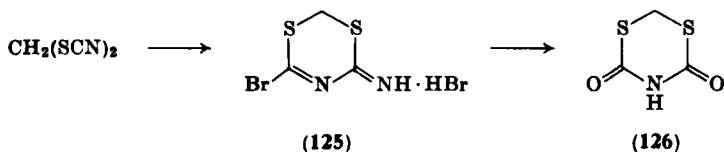
this nitrile behaves differently with hydrogen chloride and affords **123**.⁹⁷ In the presence of thiolacetic acid, 2-imino-6-thioxopiperidine hydrobromide (**124**) is formed.⁹⁸ Very little of the chemistry of these halo-bisimines has been investigated, although some work along these lines is being pursued in the Dow laboratory.



The action of hydrogen chloride on adiponitrile has been the subject of an extensive study by Zil'berman and his associates. Much of the work has been reviewed.⁹⁹ No cyclic compounds were observed with this dinitrile or its β -methyl homolog. The action of other halogen acids on adiponitriles has not been investigated. Higher aliphatic α,ω -dinitriles have received no attention.

2. 4H-1,3,5-Dithiazines

The action of hydrogen bromide on methylene bithiocyanate in ether or acetic acid produces, almost instantaneously, a quantitative yield of the moisture-sensitive 6-bromo-4-imino-4H-1,3,5-dithiazine hydrobromide (**125**), which is converted to the novel imide (**126**) when allowed to stand in water. Ethane 1,1-bisthiocyanate behaves similarly.⁹⁴



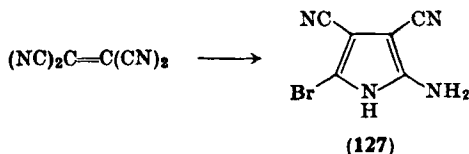
B. AROMATIC RING SYSTEMS

The cyclization lends itself to the preparation of a number of heterocyclic systems. The reactions are characterized by their good yields, and simple experimental procedure.

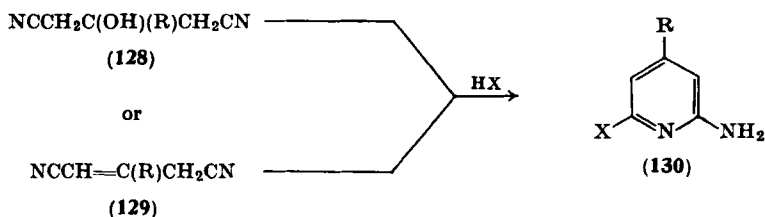
⁹⁹ E. N. Zil'berman, *Russ. Chem. Rev. (Engl. Transl.)* **31**, 615 (1962).

1. Pyrroles and Pyridines

Although the 1-pyrroline derivatives discussed above can be regarded as tautomers of 2-amino-5-halopyrrole salts, spectroscopic evidence does not support such an assignment.⁹³ Ostensibly the only true pyrrole that has been prepared¹⁰⁰ by this method is **127**, from the action of hydrogen bromide on tetracyanoethylene or tetracyanoethane. With the former material, reduction to tetracyanoethane occurs before cyclization. The product is acidic and N-alkylation of the sodium salt of **127** occurs easily on both the ring nitrogen atom and the amino group.



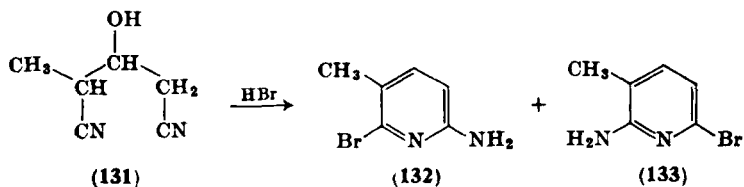
The preparation of pyridine compounds from α,ω -dinitrile systems has been studied by several workers. Johnson *et al.*¹⁰¹ found that 3-hydroxyglutaronitriles (**128**) or glutacononitriles (**129**) react readily with anhydrous hydrogen bromide or iodide to yield the 2-amino-6-halopyridines (**130**) as their salts, although in no case does hydrogen chloride cause cyclization to the expected 2-amino-6-chloropyridine.



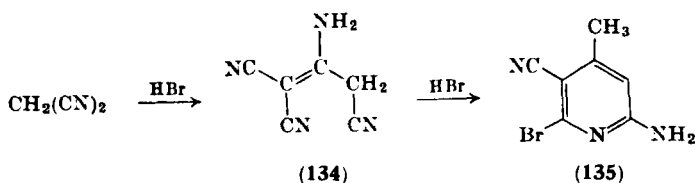
Simple alkyl substitution in **128** does not influence the course of cyclization, since **131** yields an equimolar mixture of **132** and **133**.¹⁰¹

¹⁰⁰ W. J. Middleton, V. A. Engelhardt, and B. S. Fisher, *J. Am. Chem. Soc.* **80**, 2822 (1958).

¹⁰¹ F. Johnson, J. P. Panella, A. A. Carlson, and D. H. Hunneman, *J. Org. Chem.* **27**, 2473 (1962).

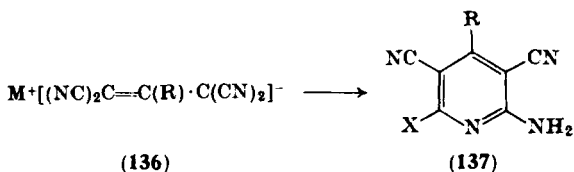


The cyclization of malononitrile and malononitrile dimer (134) by hydrogen bromide was examined by R. A. Carboni *et al.*,¹⁰² who obtained 2-bromo-3(or 5)-cyano-2,4-diaminopyridine. This, in view



of the direction of cyclization of 2-cyano-benzyl cyanide discussed below (Section III, B. 2), must be assigned the first structure (135). Hydrogen chloride affords 134 from malononitrile but again does not effect cyclization.

In the case of the salts of the tetracyanopropenes (136), however, cyclization can be effected¹⁰³ by any of the halogen acids (hydrogen fluoride is questionable as it was not tried) and leads to the highly substituted pyridines (137). The reactions are so facile that water may



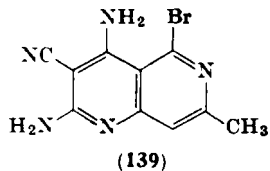
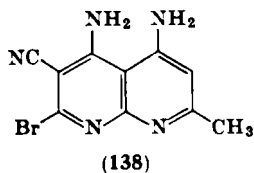
be used as the solvent. However, when acetone is used as the cyclization medium for 136 (R = NH₂), a different product is obtained which may be either 138 or 139. The latter is favored since it was not found possible to convert 137 (R = NH₂) into the naphthyridine (138), with

¹⁰² R. A. Carboni, D. D. Coffman, and E. G. Howard, Jr., *J. Am. Chem. Soc.* **80**, 2828 (1958).

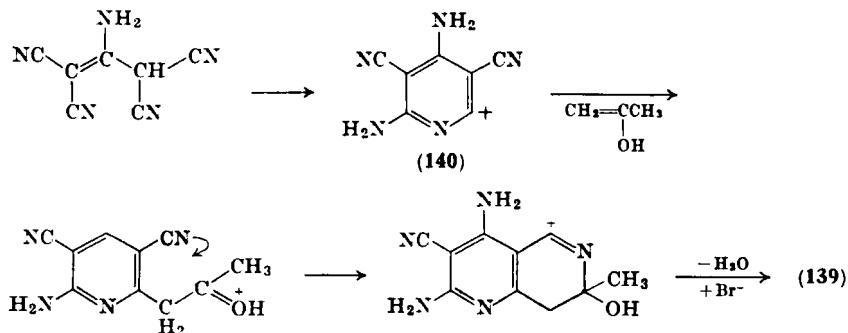
¹⁰³ E. L. Little, W. J. Middleton, D. D. Coffman, V. A. Engelhardt, and G. N. Sausen, *J. Am. Chem. Soc.* **80**, 2832 (1958).

TABLE X. PYRIDINES PREPARED BY HYDROGEN HALIDE CYCLIZATION OF 1,3-DINITRILES

| Dinitrile | HX | Pyridine | Yield (%) | Reference |
|---|-----|--|-----------|-----------|
| $\text{CH}_2(\text{CN})_2$ | HBr | 2,4-Diamino-6-bromo-3(or 5)-cyano- | 72 | 102 |
| $\text{NCCH}_2\text{CH}(\text{OH})\text{CH}_2\text{CN}$ | HBr | 2-Amino-6-bromo- | 70 | 101 |
| | HI | 2-Amino-6-iodo- | 90 | 101 |
| $\text{NCCH}_2\text{C}(\text{CH}_3)(\text{OH})\text{CH}_2\text{CN}$ | HBr | 2-Amino-6-bromo-4-methyl- | 87.5 | 101 |
| | HI | 2-Amino-6-iodo-4-methyl- | 88 | 101 |
| $\text{NCCH}_2\text{C}(\text{C}_2\text{H}_5)(\text{OH})\text{CH}_2\text{CN}$ | HBr | 2-Amino-6-bromo-4-ethyl- | 65 | 101 |
| | HI | 2-Amino-6-iodo-4-ethyl- | 85 | 101 |
| $\text{NCCH}_2\text{C}(\text{C}_6\text{H}_5)(\text{OH})\text{CH}_2\text{CN}$ | HBr | 2-Amino-6-bromo-4-phenyl- | 75 | 101 |
| | | 2-Amino-6-iodo-4-phenyl- | 54 | 101 |
| $\text{HOC}(\text{CH}_2\text{CN})_3$ | HBr | 2-Amino-6-bromo-4-carbethoxymethyl- | 51 | 101 |
| | | 2-Amino-6-bromo-3-methyl- | 56 | 101 |
| $\text{NCCH}_2\text{CH}(\text{OH})\text{CH}(\text{CH}_3)\text{CN}$ | HBr | 2-Amino-6-bromo-5-methyl- | | |
| $\text{NCCH}_2\text{CH}=\text{CHCN}$ | HBr | 2-Amino-6-bromo- | 57.5 | 101 |
| | HI | 2-Amino-6-iodo- | 17 | 101 |
| $(\text{NC})_2\text{C}=\text{C}(\text{NH}_2)\text{CH}_2\text{CN}$ | HBr | 2,4-Diamino-6-bromo-3(or 5)-cyano- | — | 102 |
| $\text{Na}[(\text{NC})_2\text{C}=\text{CHC}(\text{CN})_2] \cdot \text{H}_2\text{O}$ | HCl | 2-Amino-6-chloro-3,5-dicyano- | 90 | 103 |
| | HBr | 2-Amino-6-bromo-3,5-dicyano- | 93.5 | 103 |
| $\text{Na}[(\text{NC})_2\text{C}=\text{C}(\text{OEt})\text{C}(\text{CN})_2]$ | HCl | 2-Amino-6-chloro-3,5-dicyano-4-ethoxy- | 77.5 | |
| $[(\text{CH}_3)_4\text{N}][(\text{NC})_2\text{C}=\text{C}(\text{CN})\text{C}(\text{CN})_2]$ | HCl | 2-Amino-6-chloro-3,4,5-tricyano- | 69.5 | 103 |
| | HBr | 2-Amino-6-bromo-3,4,5-tricyano- | 90 | 103 |
| $[(\text{CH}_3)_4\text{N}][(\text{NC})_2\text{C}=\text{C}(\text{C}_6\text{H}_5)\text{C}(\text{CN})_2]$ | HCl | 2-Amino-6-chloro-3,5-dicyano-4-phenyl- | 87.5 | 103 |
| $[(\text{CH}_3)_4\text{N}][(\text{NC})_2\text{C}=\text{C}(p\text{-C}_6\text{H}_4\text{N}(\text{Me})_2)\text{C}(\text{CN})_2]$ | HCl | 2-Amino-6-chloro-3,5-dicyano-4-(<i>p</i> -dimethylaminophenyl)- | 86 | 103 |
| $\text{Na}[(\text{NC})_2\text{C}=\text{C}(\text{NH}_2)\text{C}(\text{CN})_2]$ | HCl | 2-Amino-6-chloro-3,5-dicyano-4-dimethylamino- | 10 | 103 |
| $[(\text{NC})_2\text{C}=\text{C}(\text{NH}_2)\text{C}(\text{CN})_2]^-$ 1-methylquinolinium salt | HCl | 2,4-Diamino-6-chloro-3,5-dicyano- | 52 | 103 |
| | HBr | 2,4-Diamino-6-bromo-3,5-dicyano- | 82 | 103 |
| | HI | 2,4-Diamino-6-iodo-3,5-dicyano- | 72 | 103 |
| $[(\text{NC})_2\text{C}=\text{C}(\text{Br})\text{C}(\text{CN})_2]^-$ 1-methylquinolinium salt | HBr | 2-Amino-4,6-dibromo-3,5-dicyano- | 93 | 103 |



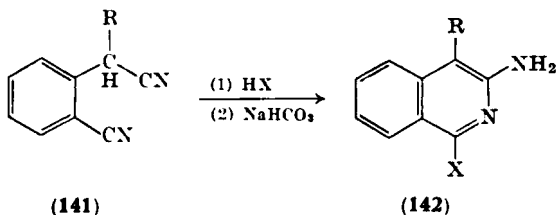
acetone and hydrogen bromide. The mechanism for the formation of **139** is envisaged as proceeding through the intermediate **140**. Such



work as has been done on the mechanism of cyclization (Section III, D) supports this view. Pyridines prepared by this procedure are listed in Table X.

2. Isoquinolines

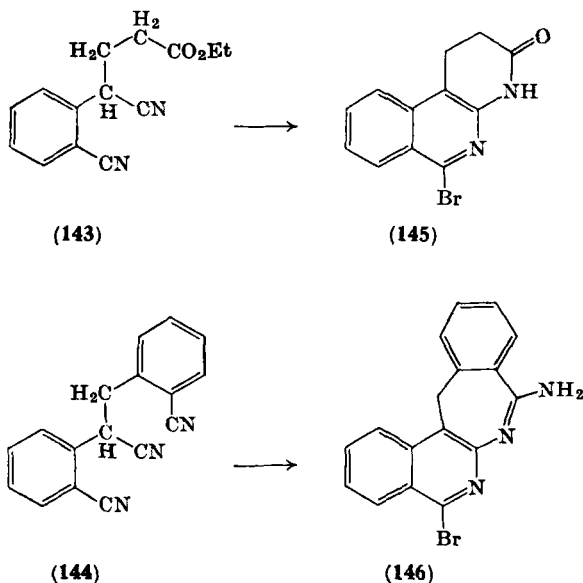
The reaction is also applicable to the preparation of the isoquinoline nucleus¹⁰⁴ by the use of 2-cyanobenzyl cyanides(**141**). The products,



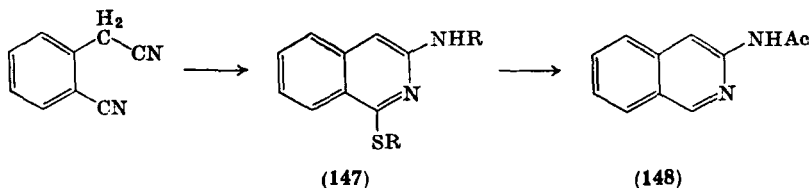
which are the result of cyclization in one specific direction, have structure **142**. Once again hydrogen bromide and iodide are effective, whereas hydrogen chloride does not cause any cyclization.

¹⁰⁴ F. Johnson and W. A. Nasutavicius, *J. Org. Chem.* **27**, 3953 (1962).

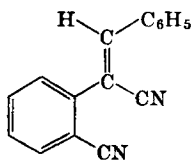
In certain instances where R (**141**) contains a carbethoxy or nitrile group, further cyclization may occur. Treatment of **143** or **144** with hydrogen bromide affords **145** and **146**, respectively, after neutralization of the intermediate salts. If the cyclization is carried out in acetic



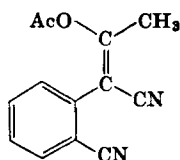
acid in the presence of a thiol, the product that is obtained depends on the reaction time.⁹⁴ After a short period **147** ($R' = H$) results, but if the reaction mixture is allowed to stand, acetylation occurs and high yields of **147** ($R' = Ac$) can be isolated. Desulfurization of **147** ($R = C_6H_5$; $R' = Ac$) leads to 3-acetamidoisoquinoline (**148**), confirming the position of the $RS-$ group. Not all of the dinitriles



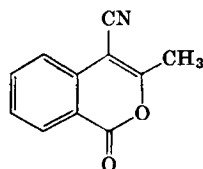
examined led to the expected products.¹⁰⁴ Treatment of **149** with hydrogen bromide affords only intractable gums, whereas **150** yields the isocoumarin (**151**). Isoquinolines formed by this cyclization procedure are listed in Table XI.



(149)



(150)



(151)

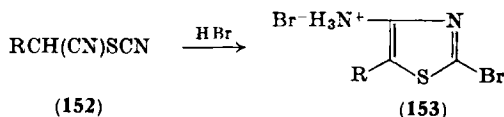
TABLE XI

ISOQUINOLINES FROM HYDROGEN HALIDE CYCLIZATION OF
2-NCC₆H₄CH(R)CN

| R | HX | Isoquinoline | Yield (%) |
|---|-----|------------------------------|-----------|
| H | HBr | 3-Amino-1-bromo- | 66 |
| H | HI | 3-Amino-1-iodo- | 74 |
| CH ₃ | HBr | 3-Amino-1-bromo-4-methyl- | 80 |
| C ₂ H ₅ | HBr | 3-Amino-1-bromo-4-ethyl- | 92 |
| C ₆ H ₅ CH ₂ | HBr | 3-Amino-1-bromo-4-benzyl- | 88 |
| C ₆ H ₅ CH ₂ | HI | 3-Amino-1-iodo-4-benzyl- | 52 |
| C ₆ H ₅ CH ₂ CH ₂ | HBr | 3-Amino-1-bromo-4-phenethyl- | 95 |
| C ₆ H ₅ CH ₂ CH ₂ | HI | 3-Amino-1-iodo-4-phenethyl- | 80 |
| | HBr | 3-Amino-1-bromo-7-nitro- | 78 |

3. Thiazoles and Selenazoles

When the cyclization procedure, using hydrogen bromide, is applied to α -cyanoalkyl thiocyanates (**152**), the salts of 2-bromo-4-aminothiazoles (**153**) can be obtained in excellent yield.¹⁰⁵ Most of these salts



are moisture-sensitive, undergoing decomposition very easily. Isolation of the free bases thus proved very difficult and it was more expedient to add acetic anhydride to the cyclization product and obtain the thiazoles as the 4-acetamido derivatives (Table XII).

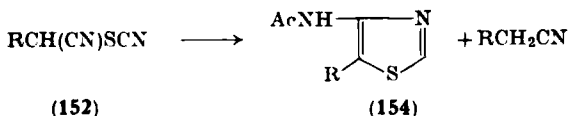
¹⁰⁵ F. Johnson and W. A. Nasutavicus, *J. Org. Chem.* **28**, 1877 (1963).

TABLE XII

THIAZOLES FROM HYDROGEN HALIDE CYCLIZATION OF $RCH(CN)SCN$

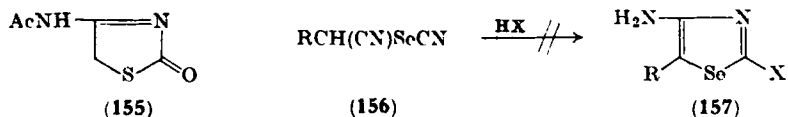
| R | HX | Thiazole | Yield (%) |
|-------------------|-----|--|-----------|
| H | HBr | 4-Acetamido-2-bromo- | 86 |
| H | HI | 4-Acetamido- | 24 |
| C_3H_7 | HBr | 4-Acetamido-2-bromo-5-propyl- | 43 |
| C_6H_5 | HBr | 4-Acetamido-2-bromo-5-phenyl- | 74 |
| 2- ClC_6H_4 | HBr | 4-Acetamido-2-bromo-5-(2-chloro-phenyl)- | 55 |
| 4- ClC_6H_4 | HBr | 4-Acetamido-2-bromo-5-(4-chloro-phenyl)- | 80 |
| 2,4- $Cl_2C_6H_3$ | HBr | 4-Acetamido-2-bromo-5-(2,4-dichloro-phenyl)- | 94 |
| 2,4- $Cl_2C_6H_3$ | HI | 4-Acetamido-5-(2,4-dichlorophenyl)- | 25 |
| 2-MeOC $_6H_4$ | HBr | 4-Acetamido-2-bromo-5-(2-methoxy-phenyl)- | 83 |
| 2- $NO_2C_6H_4$ | HBr | 4-Acetamido-2-bromo-5-(2-nitro-phenyl)- | 20 |
| 4-AcNHC $_6H_4$ | HBr | 4-Acetamido-2-bromo-5-(4-acetamido-phenyl)- | 88 |

Cyclization of **152** with hydrogen iodide in acetic acid is more complicated and proceeds with concomitant reduction (of the iodo group) and acetylation, the final product being **154**. With this reagent some



cleavage of the thiocyanate group occurs also, for it was possible to isolate 2,4-dichloro-phenylacetonitrile when **152** ($R = 2,4\text{-Cl}_2C_6H_3$) was cyclized.

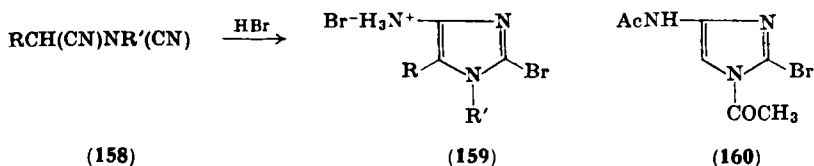
The action of hydrogen chloride on **152** ($R = H$) led only to a chlorine-free product which was assigned structure **155**. Attempts to prepare selenazoles by the action of halogen acids on α -cyanoalkyl



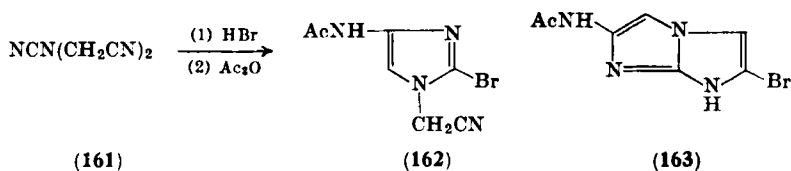
selenocyanates (**156**) met with comparative failure. Only in the case of **156** ($R = 2,4\text{-Cl}_2\text{C}_6\text{H}_3$) was a minute yield of a product isolated after acetylation, and the structural assignment (**157**, $R = 2,4\text{-Cl}_2\text{C}_6\text{H}_3$) is based only on spectral evidence.

4. Imidazoles

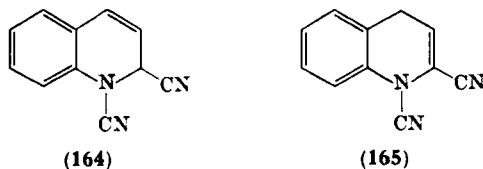
The synthesis of imidazoles has also been effected using this cyclization procedure.¹⁰⁶ The synthesis which is analogous to that of the thiazole case utilizes α -cyanoalkyl cyanamides (**158**) and yields products having the structure **159**. Hydrogen bromide, only, was used



as the cyclizing agent. Here once again the salts (**159**) are moisture-sensitive, but to a lesser degree than those of the corresponding thiazoles. Again, it often proved more expedient to acetylate the amino group to facilitate isolation.



It was not possible to prepare the parent compound (**159**, $R = R' = \text{H}$), due to the inaccessibility of pure α -cyanomethyl cyanamide. Cyclization of a crude specimen of the latter substance followed by acetylation led to a low yield of **160**. The action of hydrogen bromide on **161** gives **162** and not a six-membered ring or a bicyclic compound such as **163**. Attempts to cyclize **164** and **165** proved

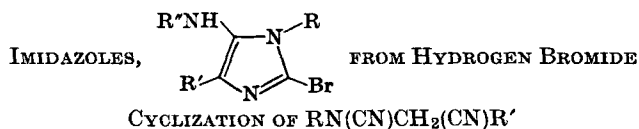


¹⁰⁶ F. Johnson and W. A. Nasutavicius, *J. Org. Chem.* **29**, 153 (1964).

fruitless. Doubtless if the heterocyclic ring were saturated, cyclization would occur normally. However, selective reduction of the double bond of neither of these compounds has been accomplished so far.⁹⁴

Imidazoles prepared by this method are listed in Table XIII.

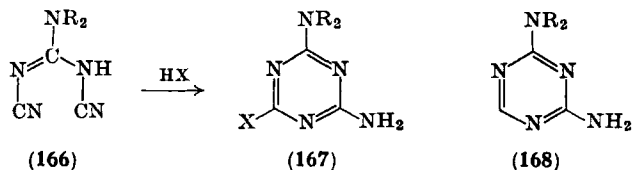
TABLE XIII



| R | R' | R'' | Yield (%) |
|---|---|--------------------|-----------|
| CH ₃ | H | CH ₃ CO | 33 |
| C ₂ H ₅ | H | CH ₃ CO | 53 |
| C ₄ H ₉ | H | CH ₃ CO | 47 |
| CH ₂ CN | H | CH ₃ CO | 5-65 |
| C ₆ H ₅ | H | CH ₃ CO | 82 |
| C ₆ H ₅ | C ₆ H ₅ | H | 82 |
| C ₆ H ₅ | 2-ClC ₆ H ₄ | H | 10 |
| C ₆ H ₅ | 2-ClC ₆ H ₄ | CH ₃ CO | 55 |
| C ₆ H ₅ | 4-ClC ₆ H ₅ | CH ₃ CO | 50 |
| C ₆ H ₅ | 2,4-Cl ₂ C ₆ H ₃ | H | 68 |
| C ₆ H ₅ | 2-CH ₃ OC ₆ H ₄ | H | 82.5 |
| C ₆ H ₅ CH ₂ | H | CH ₃ CO | 68 |

5. Triazines

The preparation of derivatives (167) of this ring system by the action of halogen acids on dicyanoguanidines (166) was reported by Kaiser and Roemer^{107,108} in 1953. Their patents undoubtedly represent the first specific applications of dinitrile cyclization to the synthesis of a heterocyclic system. Excellent yields of 167 were



¹⁰⁷ J. J. Roemer and D. W. Kaiser, U.S. Patent 2,658,893 (1953).

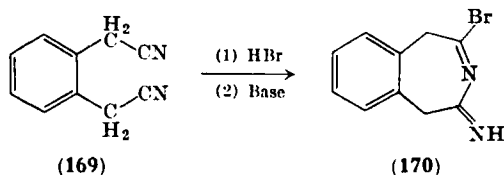
¹⁰⁸ D. W. Kaiser and J. J. Roemer, U.S. Patent 2,630,433 (1953).

obtained with concentrated *aqueous* solutions of hydrogen chloride, bromide, or iodide and thus the cyclization is closely related to that reported by Pellizzari,⁹⁰ whereby concentrated hydrochloric acid converts **112** to **113**.

If the dicyanoguanidine is added to constant boiling hydriodic acid at 90–100°, the reductive cleavage of the iodo-group of **167** occurs and **168** is obtained, but the yields are poor.

C. SEVEN-MEMBERED RINGS

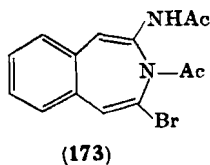
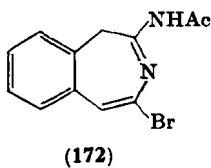
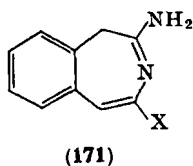
In 1959, Osborn⁹³ reported that the action of hydrogen bromide on *o*-phenylene diacetonitrile (**169**) in ether led to the bromo-bisimine (**170**) as its hydrobromide. Infrared evidence was cited in support of



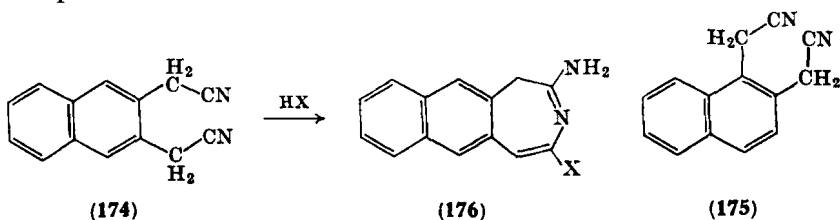
this structure. Independently, the cyclization of **169** had been studied in the author's laboratory¹⁰⁹ and the comparative lack of sensitivity of the product to mild base was noted. This is in marked contrast to the corresponding cyclization products of succinonitrile and glutaronitrile, both of which have essentially the same type of halo-bisimine group and which are hydrolyzed with great ease. Recently the cyclization product of **169** has been re-examined by means of proton NMR (60 Mc/S) spectroscopy.¹¹⁰ This indicates the presence of only one $\text{—CH}_2\text{—}$ group at -227.5 cps and a vinyl hydrogen (-432 cps). Hydrogenation of **170** under mild conditions leads to a debrominated product whose NMR spectrum reveals two vinyl protons splitting each other at -382 and -415 cps, an amino group at -291 cps, and a $\text{—CH}_2\text{—}$ group at -193 cps. If it is assumed that no deep-seated shifts of the double bonds occur on reduction, then the base of the initial cyclization product must be **171** ($\text{X} = \text{Br}$), not **170**, and its hydrogenation product (**171**, $\text{X} = \text{H}$). The chemistry of **171** ($\text{X} = \text{Br}$)

¹⁰⁹ F. Johnson and W. A. Nasutavicius, *J. Heterocyclic Chem.* **2**, 26 (1965).

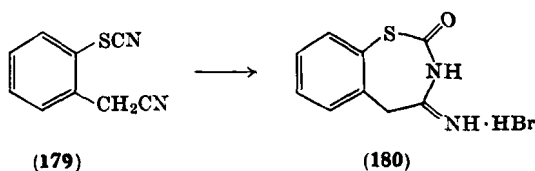
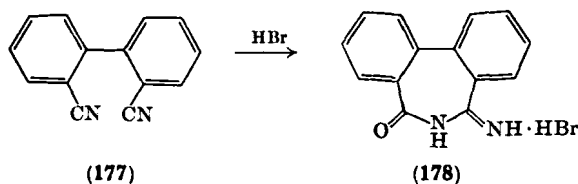
¹¹⁰ Measurements were made at 60 Mc/S, with respect to TMS as an internal standard at 0 cps; **170** was measured in CDCl_3 and **171** ($\text{X} = \text{H}$) in $\text{CDCl}_3/\text{CF}_3\text{CO}_2\text{H}$.



is still under investigation. Its reactions are interesting since it behaves to some degree as an amidine, whereas the halogen atom has approximately the reactivity of that of 2-bromopyridine. Acetylation leads to **172** at room temperature,¹⁰⁹ but to the true azepine (**173**) at temperatures over 100°



The cyclization reaction is not confined to **169**. Both **174** and **175** undergo cyclization to seven-membered ring compounds.¹⁰⁹ The former affords **176**, whereas the latter leads to a mixture from which



only one of the two expected dihydroazepine compounds can be isolated in a pure state. The exact structure of the latter has not been determined.

The cyclization of **177** could be effected only in acetic acid, and the sole product isolated thus far is **178**. Attempts to obtain a halo-bisimine from **177** in other media have been unsuccessful (see, however, Reference 109). The behavior of **179** is similar to that of **177**, solely **180** having been obtained to date.¹¹⁰ Further investigations using other 1,4-dicyano compounds are in progress in the Dow laboratory.

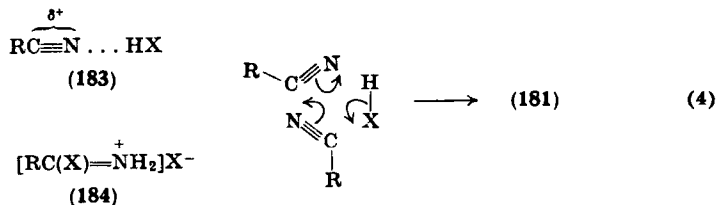
D. MECHANISM OF DINITRILE CYCLIZATION

The action of halogen acids on nitriles has received a considerable amount of attention, especially with regard to hydrogen chloride. Much of the literature has been reviewed by Zil'berman,⁹⁹ whose own work has helped to clarify some of the complexities of this area.

The dimerization of nitriles, of which dinitrile cyclization appears to be a special case, was studied by Grundmann and his co-workers.¹¹¹ They convincingly demonstrated that these compounds have the structure **181** or **182**. Lazaris *et al.*¹¹² have suggested that the



mechanism of formation of the dimers involves electrophilic attack of an outer nitrile complex⁸⁶ (**183**) on the nitrogen atom of an unattached nitrile. In addition, Zil'berman⁹⁹ has put forward a cyclic electron transfer reaction (Eq. 4) as an alternative. These workers were

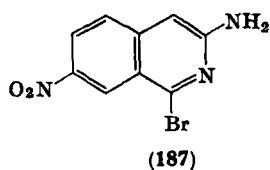
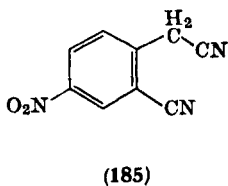
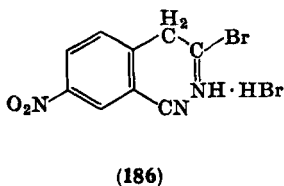


¹¹¹ C. Grundmann, G. Wiese, and S. Seide, *Ann.* **577**, 77 (1952).

¹¹² A. Ya. Lazaris, E. N. Zil'berman, and O. D. Strizhakov, *Zh. Obshch. Khim.* **32**, 900 (1962).

able to show also that, in certain instances, dimer formation is a result of operating at room temperature and that at lower temperatures (-50 to -5°) the halogenoimmonium halides (**184**) are formed. These are reputedly destabilized at higher temperatures by loss of hydrogen halide, whereby the equilibrium shifts toward the formation of the initial reactants which then give rise to dimers. The possibility that dimers could be formed by the nucleophilic attack of the nitrile on **184** or the imino halide $RC(X)=NH$ does not appear to have been considered.

In the light of the above work, an attempt¹¹³ was made to isolate a salt such as **184** from the action of hydrogen bromide on **185** at low temperatures. Since it is a well-known, but seldom stated, fact that aliphatic nitriles are more sensitive to attack by acids than are their aromatic counterparts, the product expected was **186**. In using **185**, it was hoped that the nitro group would to some extent deactivate the

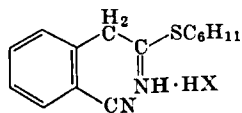


aromatic nitrile and inhibit its interaction with the adjacent bromoimmonium salt. (The more desirable 2-cyano-5-nitrobenzyl cyanide is experimentally inaccessible.) However, either **185** did not react at the temperatures used or the cyclized product (**187**) was obtained, and no intermediate compound could be obtained.

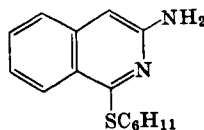
In view of this, recourse was made to an examination of the reaction of 2-cyanobenzyl cyanide (**141**, $R = H$) with a thiol in the presence of a halogen acid. Here some interesting results were obtained. In an acetic acid-ether medium **141** ($R = H$) rapidly reacted with cyclohexyl thiol under the influence of hydrogen bromide or chloride to give a highly crystalline salt. The latter compound must be assigned structure **188** ($X = Cl$ or Br) since its infrared spectrum compares closely with that of the corresponding salt from benzyl cyanide but not with that from benzonitrile. In addition an aromatic nitrile group was still evident at 4.46μ .

¹¹³ F. Johnson and D. H. Hunneman, Unpublished results (1962).

When **188** ($X = \text{Cl}$) was heated in acetic acid either with or without one equivalent of sodium acetate, the isoquinoline (**189**) was formed. The free base **190** of **188** could be isolated by neutralization with mild alkali and, as with most imino thioethers, slowly reverted to



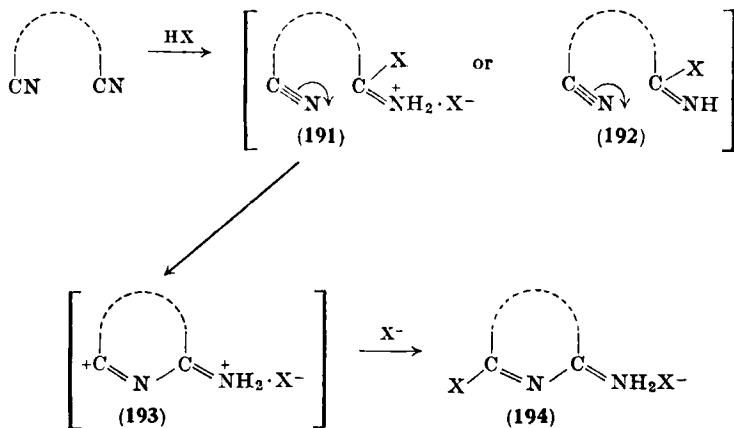
(188)



(189)

cyclohexyl thiol and the 2-cyanobenzyl cyanide on standing. Surprisingly, however, when **190** was heated in an inert medium, **189** was again produced. This reaction is interpreted as involving a nucleophilic attack by the nitrile group on the imino thioether and appears to be a rather novel demonstration of the nucleophilic properties of a nitrile group in an essentially neutral system.

In the case of the ring closure of **188**, a similar path is probably followed, the presence of a positive charge on the imine nitrogen serving to hasten the cyclization. In the latter system isoquinoline formation occurs at room temperature. Because the leaving group capabilities of an alkylthio appear to be about the same as those of a bromine atom, when attached to an sp^2 carbon, it seems likely that the mode of cyclization of dinitriles under the influence of hydrogen bromide or iodide follows a course (Eq. 5) similar to that of the ring



closure of **188**. The question as to why hydrogen chloride, for the most part, does not effect such cyclizations still requires an answer. One reason might be that the carbon-to-chlorine bond strength in the initial complex (**191** or **192**, $X = Cl$) is too high to permit the facile displacement of chlorine by another nitrile group. Treatment with base, as is usually done in the workup, might then be expected to regenerate the dinitrile. This would explain the apparent lack of reaction.

An alternate and better explanation may lie in the fact that if the positively charged **193** ($X = Cl$) is formed using hydrogen chloride, it (or its nitrilium salt equivalent) may not always be able to polarize the chlorine atom (in HCl) or ion sufficiently to effect formation of **194** ($X = Cl$). Some evidence for the latter view has been obtained by attempting to cyclize 2-cyanobenzyl cyanide in acetic acid (**141**, $R = H$) using small amounts of hydrogen bromide as an initiator in the presence of a large excess of hydrogen chloride. Although a product was obtained, none of the desired 1-chloro-3-amino-isoquinoline could be isolated. The former is still under investigation. Interestingly, though, the treatment of **188** with an excess of hydrogen bromide in acetic acid led to 1-bromo-3-aminoisoquinoline, indicating that competition between two fairly polarizable groups is possible.

One last comment concerning the direction of ring closure should be made. It appears that, in a mixed system involving an aliphatic nitrile and a nitrile attached to any group other than aliphatic, when cyclization takes place the former nitrile is destined to give rise to the amino group and the latter to bear the halogen atom. This undoubtedly reflects the difference in basic character between the two nitriles involved. So far, the relative basicities of various types of nitriles have not been studied. Thus the direction of cyclization of α,ω -dinitrile systems, other than those in the above category, cannot be predicted with certainty. Some work aimed at investigating this point and at further clarification of the mechanism of this cyclization is being pursued by one of the authors and his associates at Wayland.

Cyclic Enamines and Imines

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I. Introduction

In this review, the properties, methods of preparation, and reactions of heterocyclic compounds possessing the so-called enamine grouping, *viz.* compounds with the three-atom system $\text{—}\ddot{\text{N}}\text{—C=C—}$ in which at least the nitrogen atom is part of a ring, are discussed. In a stricter

sense, only those compounds should be designated as "heterocyclic enamines" which contain all three of the atoms in question in their ring system, *viz.* pyrrolines and piperideines. Such a limitation would lead to a narrow field for consideration. We shall, therefore, also include the reactions of enamines obtained from aliphatic or alicyclic carbonyl compounds and those from secondary heterocyclic bases, which are very interesting from the preparative point of view.

The typical behavior of enamines has been mainly observed for compounds possessing a tertiary nitrogen atom.¹ The analogous derivatives with a secondary amino group (the α,β -unsaturated secondary amines) could, in principle, possess either the imino or the tautomeric enamine structure, but the first possibility is preferred practically without exception. In the text, some examples of their properties are quoted for the sake of comparison with those of tertiary enamines; on these occasions, the group designation "imines" is used. Nucleophilic reactions of a limited number of aromatic heterocyclic systems are also included when they are similar to the reactions of enamines and illustrate the specific character of the enamine grouping.

In the first part of the review, the structure and physico-chemical properties of enamines are discussed. Subsequent sections deal with the methods of preparation and chemical reactivity and are systematically classified according to the mechanism rather than according to their preparative value.

II. Structure and Physicochemical Properties

A. STRUCTURE OF ENAMINES

The existence of an enamine grouping in a molecule makes possible several interconvertible isomeric structures. This fact is responsible for the high reactivity of these compounds. Their use in organic syntheses and their relatively frequent appearance in nature have stimulated a continuing intensive study of their structure.

Unsaturated amines in which the double bond is separated from the nitrogen atom by at least one saturated carbon atom show behavior typical of saturated amines and non-conjugated olefins. A double bond in the position α,β to the nitrogen atom leads, by contrast, to the formation of a new reactive grouping in which the free electron pair of nitrogen is conjugated with the π -electrons of the double bond. The character of both the original structural elements is considerably

¹ N. J. Leonard and F. P. Hauck, *J. Am. Chem. Soc.* **79**, 5279 (1957).

changed. The shift of the free electron pair according to the mesomeric formulae



leads to a polarized structure with a positive charge on the nitrogen atom, i.e. to an immonium cation. The mesomeric character is then exemplified by the fact that reactions may occur on either the nitrogen or carbon atoms of the grouping, an increased basicity of the molecule, and a change in the spectral properties of the double bond. The full consequences of the mesomerism are to be expected particularly with the tertiary amines.

1. Secondary Enamines

If one of the substituents on the nitrogen is a hydrogen atom, a tautomeric equilibrium between the enamino and imino forms² must be taken into account. In the majority of the hitherto reported cases, the equilibrium is strongly in favor of the imino form of the aliphatic as well as the cyclic compounds.³ However, the predominance of the imino form could be precluded by the possibility of formation of a highly conjugated system of double bonds with the free electron pair on the nitrogen atom. This holds also for heterocyclic enamines with a secondary amino group. Beginning with Gabriel⁴ and Hilscher,⁵ until recently, authors generally formulated the characteristic representatives of this class of compounds with a double bond in the Δ^2 -position with respect to the nitrogen atom in spite of the lack of evidence for this formulation. The former confidence of most authors in the Δ^2 -pyrroline structure is very curious⁶ in view of the rare occurrence of aliphatic vinylamines. Sonn⁷ and Cloke and Leary⁸ were the first to consider the tautomeric relationship between Δ^1 - and Δ^2 -pyrrolines. According to physical measurements, the occurrence of Δ^2 -pyrrolines unsubstituted on the nitrogen atom is very improbable, even with 2-arylpyrrolines where there is a possibility of fixation of the Δ^2 -structure by conjugation with the aromatic ring. In fact, a very strong band

² A. Seher, *Arch. Pharm.* **284**, 371 (1951); *Chem. Abstr.* **47**, 2123 (1953).

³ G. Opitz, H. Hellmann, and H. W. Schubert, *Ann. Chem.* **623**, 117 (1959).

⁴ S. Gabriel, *Ber.* **42**, 1238 (1909).

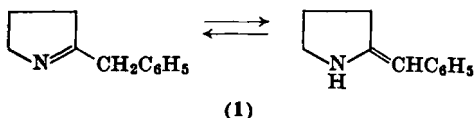
⁵ R. Hilscher, *Ber.* **31**, 277 (1898).

⁶ J. H. Burrekhalter and J. H. Short *J. Org. Chem.* **23**, 1278 (1958).

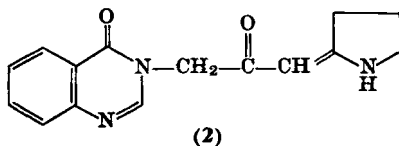
⁷ A. Sonn, *Ber.* **68**, 148 (1935).

⁸ J. B. Cloke and T. S. Leary, *J. Am. Chem. Soc.* **67**, 1249 (1945).

at 1620 cm^{-1} attributable to the carbon-nitrogen double bond has been found in the infrared spectra of many 2-arylpyrrolines [2-*p*-methoxyphenyl, 2-phenyl, 2-thienyl, 2-(4-biphenyl), 2-(9-phenanthryl), and 2-(1-naphthyl)], but absorption at 3300 cm^{-1} due to the presence of the N—H group was not present. Similar properties were observed for the alkaloid myosmine,⁹ 2- β -pyridyl- Δ^1 -pyrroline, previously thought to be the Δ^2 -isomer. Analogous results have been obtained by the Zerewitinov determination of the active hydrogen, which is negative in all cases.^{6, 10} The determination also is negative¹¹ with 2,3-diphenylpyrroline, where the likelihood of stabilization of the Δ^2 -structure is higher. It should be stated, however, that an analogous study of 3-arylpyrrolines and substituted 2-benzylpyrrolines should be more decisive in this respect. According to the active hydrogen estimation, 2-benzylpyrroline (1) seems to exist solely in the Δ^1 -form, whereas infrared spectral data point to the existence of a tautomeric mixture of the Δ^1 -form and an enamine with the exo-situated double bond.



An *N*-unsubstituted pyrroline derivative in which an exocyclic double bond has been established is compound 2.



The double bond is kept in the exocyclic position by conjugation with the carbonyl group (the free base absorbs at 3270 cm^{-1}). The free base of 1-(α -picolyl)-6,7-methylenedioxy-3,4-dihydroisoquinoline also possesses the stabilized enamine structure, whereas the imino structure is exhibited by the 1-methyl analog, as shown by comparison of the

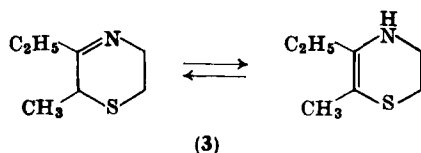
⁹ J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High-Resolution Nuclear Magnetic Resonance," p. 281. McGraw-Hill, New York, 1959.

¹⁰ M. C. Kloetzel, J. L. Pinkus, and R. M. Washburn, *J. Am. Chem. Soc.* **79**, 4222 (1957).

¹¹ P. M. Maginnity and J. B. Cloke, *J. Am. Chem. Soc.* **73**, 49 (1951).

ultraviolet spectra of the free bases and those of the protonated salts.¹² However, absorption at 3300 cm^{-1} also occurs with 2-methylpyrroline; this experimental finding has not been clarified yet. Thus, the present tendency to reject Δ^2 -structures for all compounds of the above type should be regarded with caution.

A situation analogous to that of the pyrroline derivatives also exists, according to spectroscopic data, with *N*-unsubstituted piperidine compounds. There is little experimental data because Δ^2 -piperideines have not been studied as extensively as the analogous pyrrolines. The Δ^1 -structure has been established for some aliphatically substituted piperideines, e.g., $\Delta^{1(8)}$ -hexahydropyrindene,^{12, 13} $\Delta^{1(10)}$ -octahydroquinoline,¹³ and the alkaloid γ -coniceine.^{14, 15} According to conformational considerations, structures other than Δ^1 -piperideine could be expected more frequently in the piperideine series. The thia analog¹⁶ **3** occurs in the amino form as shown by infrared spectral data and the estimation of active hydrogen.



Conjugation has a great influence on the structure of aliphatic and alicyclic compounds. Thus, the existence of an amino form has been established (in addition to the extreme case of aromatic amines¹⁷) for all compounds where the double bond is conjugated with a carbonyl group (or its equivalent),¹² with esters^{12, 18} and nitriles of α,β -unsaturated β -amino acids,^{5, 19, 20} and with β -amino-ketones. The β -keto-esters ethyl 2-cyclopentanone-1-carboxylate and ethyl 2-cyclohexanone-1-carboxylate exist as mixtures containing 95% of the keto

¹² B. Witkop, *J. Am. Chem. Soc.* **78**, 2873 (1956).

¹³ L. A. Cohen and B. Witkop, *J. Am. Chem. Soc.* **77**, 6595 (1955).

¹⁴ H. C. Beyerman, M. van Leeuwen, J. Smidt, and A. van Veen, *Rec. Trav. Chim.* **80**, 513 (1961).

¹⁵ K. H. Büchel and F. Korte, *Chem. Ber.* **95**, 2460 (1962).

¹⁶ F. Asinger, F. J. Schmitz, and S. Reichel, *Ann. Chem.* **652**, 50 (1962).

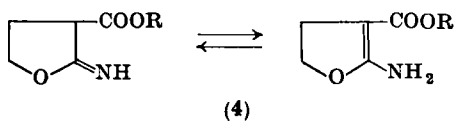
¹⁷ B. Witkop, *Experientia* **10**, 420 (1954).

¹⁸ J. D. S. Goulden, *J. Chem. Soc.* p. 997 (1953).

¹⁹ W. J. Middleton and V. A. Engelhardt, *J. Am. Chem. Soc.* **80**, 2788 (1958).

²⁰ S. Baldwin, *J. Org. Chem.* **26**, 3288 (1961).

form and 75% of the enol form,²¹ respectively; by contrast both the analogous nitrogen derivatives exist exclusively in the enamine form.¹² The keto-enol tautomerism, but not the formally analogous enamine-imine tautomerism, appears to be influenced²⁰ by conformational factors. Similarly, the imide-enamide tautomerism of derivatives of β -amino- β -ethoxyacrylic acid,²² and of the furan derivative **4**, is also relatively insensitive to conformational factors.



Notwithstanding, conformational factors apparently play a part in the enamine-imine equilibrium of the Schiff base prepared from cyclohexanone and cyclohexylamine, as shown by their infrared spectra²³: the base appears to be a mixture of both tautomeric forms, *N*-cyclohexylidenecyclohexylamine and *N*-1-cyclohexenylcyclohexylamine. Replacement of the cyclohexyl group by a phenyl group appears to stabilize the imino form.²⁴

2. Tertiary Enamines

The tertiary enamines, in contrast to the secondary derivatives, cannot exhibit enamine-imine tautomerism. As the free bases, they exist only in the vinylamino form. Their physico-chemical properties are in agreement with this structure, especially the spectral properties. The bands due to the stretching frequency of the carbon-carbon double bond in their infrared spectra^{1, 25-27} (situated at 1630-1660 cm^{-1} according to the nature of the substituents) occur at somewhat lower frequencies, but their intensities are greatly increased in comparison to those of simple olefins because of conjugation with the free electron pair on the nitrogen atom. Indications of *cis-trans* isomerism

²¹ N. J. Leonard, H. S. Gutowsky, W. J. Middleton, and E. M. Petersen, *J. Am. Chem. Soc.* **74**, 4070 (1952).

²² F. Korte and K. Trautner, *Chem. Ber.* **95**, 295 (1962).

²³ E. D. Bergmann, E. Zimkin, and S. Pinchas, *Rec. Trav. Chim.* **71**, 168 (1952).

²⁴ G. Reddelien and O. Meyn, *Ber.* **53**, 345 (1920).

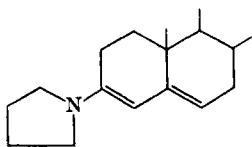
²⁵ G. Opitz and H. W. Schubert, *Angew. Chem.* **70**, 247 (1958).

²⁶ N. J. Leonard and V. W. Gash, *J. Am. Chem. Soc.* **76**, 2781 (1954).

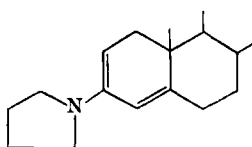
²⁷ R. Dulou, E. Elvik, and A. Veillard, *Bull. Soc. Chim. France* p. 967 (1960).

about the double bond have been observed with aliphatic enamines.²⁷ Comparison with aliphatic nitrogen-free olefins points to the existence of *trans*-structures in general.

The ultraviolet spectra^{27, 28} exhibit, in agreement with the general postulate of Braude *et al.*,^{29, 30} a bathochromic shift to 225–235 $m\mu$ caused by the auxochromic action of the nitrogen-free electron pair. This shift is approximately the same as that caused by introduction of a conjugated double bond, and is increased by further conjugation with other multiple bonds, e.g. in diene-amines prepared from Δ^4 -3-oxosteroids.^{31, 32} Spectral maxima (at 280–285 $m\mu$, ϵ 19,000–26,000) point to the conjugation of three mobile electron pairs but cannot decide the position of the double bonds; the molecular extinction coefficient indicates a transoid (5) rather than cisoid arrangement (e.g. 6).³³



(5)



(6)

The basic types of heterocyclic enamines, pyrrolines, and piperidines, unsubstituted^{20, 34} or aryl-substituted³⁵ in position 2, evidently possess an endocyclic Δ^2 -double bond. The corresponding stretching frequency can be lowered to 1620–1630 cm^{-1} by conjugation with an aromatic substituent. The double bond of the analogous heterocyclic compounds with aliphatic substituents on C(2) may occupy either the exo or the endo position. Lukeš *et al.*³⁶ have shown that the majority of the above five-membered ring compounds, traditionally formulated with a double bond in the Δ^2 -position, possess

²⁸ N. J. Leonard and D. M. Locke, *J. Am. Chem. Soc.* **77**, 437 (1955).

²⁹ K. Bowden, E. A. Braude, and E. R. H. Jones, *J. Chem. Soc.* 948 (1946).

³⁰ K. Bowden, E. A. Braude, E. R. H. Jones and B. C. L. Weedon, *J. Chem. Soc.* 45 (1946).

³¹ F. W. Heyl and M. E. Herr, *J. Am. Chem. Soc.* **75**, 1918 (1953).

³² J. L. Johnson, M. E. Herr, J. C. Babcock, A. E. Fonken, J. E. Stafford, and F. W. Heyl, *J. Am. Chem. Soc.* **78**, 430 (1956).

³³ L. Dorfman, *Chem. Rev.* **53**, 47 (1953).

³⁴ K. H. Büchel and F. Korte, *Chem. Ber.* **95**, 2465 (1962).

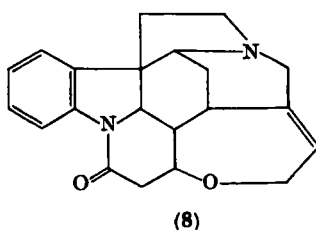
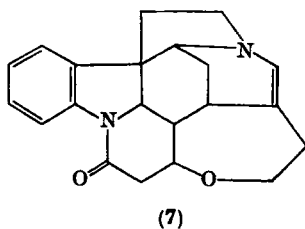
³⁵ K. H. Büchel and F. Korte, *Chem. Ber.* **95**, 2438 (1962).

³⁶ R. Lukeš, V. Dědek, and L. Novotný, *Chem. Listy* **52**, 654 (1958); *Collection Czech. Chem. Commun.* **24**, 1117 (1959).

the structure of 2-alkylidene derivatives with an exocyclic double bond absorbing at 1677 cm^{-1} . Only the 1,2-dimethyl derivative is actually a Δ^2 -pyrroline absorbing at 1632 cm^{-1} . Similarly, the pyrroline system of the holarrhena alkaloids^{36a} (conkurchine and conesidine) possesses an endocyclic rather than an exocyclic double bond³⁷

TABLE I
THE COMPARATIVE BASICITIES OF NEOSTRYCHNINE AND
RELATED COMPOUNDS

| Base | pK_a at 20°C in 80% methylcellosolve |
|-------------------|---|
| Neostrychnine (7) | 3.8 |
| Strychnine (8) | 7.37 |
| Dihydrostrychnine | 7.45 |



On the other hand, 1-methylpiperideines possess a fixed^{38, 39} endocyclic double bond ($\nu_{C=C}$ $1635\text{--}1645\text{ cm}^{-1}$) in agreement with Brown's generalization⁴⁰ about the relative stability of double bonds in five- and six-membered rings.

The above mentioned mesomerism between a polarized and a non-polarized structure of enamines possessing a tertiary nitrogen atom is reflected in their physical properties and chemical reactivity. For

^{36a} A semiquantitative procedure has been worked out³⁷ by Tschesche and Snatzke for estimation of the number of methyl groups in this type of compound which involves determination of the integrated absorption of the band at $1350\text{--}1390\text{ cm}^{-1}$. The methyl groups bound on the pyrroline nucleus are also detectable by this procedure.

³⁷ R. Tschesche and G. Snatzke, *Chem. Ber.* **90**, 579 (1957).

³⁸ O. Červinka, *Collection Czech. Chem. Commun.* **25**, 1174 (1960).

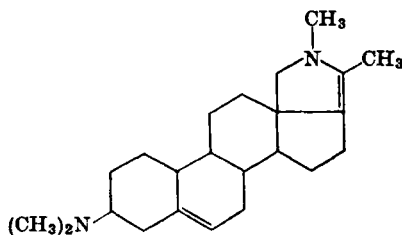
³⁹ O. Červinka, *Collection Czech. Chem. Commun.* **25**, 2675 (1960).

⁴⁰ H. C. Brown, *J. Org. Chem.* **22**, 439 (1957).

mesomerism to occur, a planar arrangement is required for the $\text{—}\ddot{\text{N}}\text{—C=C—}$ atoms and the five atoms immediately bound to this system. If the condition of planarity is not fulfilled, full interaction of the π -electrons of the double bond with the free electron pair on the nitrogen atom is not possible. In extreme cases, the compounds do not show the properties characteristic of enamines, and here the mutual inductive effect of the nitrogen atom and the double bond may be observed without the complicating consequences of mesomerism.

Steric hindrance of the mesomerism occurs mainly in polycyclic systems. The basicity of such compounds is decreased^{37, 41, 42} in comparison to that of analogous saturated bases or bases with a more distant double bond. Neostrychnine may serve as an example (Table I).

Further, the ultraviolet absorption of compounds of this kind does not show the characteristic bathochromic shift. Thus, e.g., trimethylconkurchine (9) shows the same absorption as the corresponding saturated tertiary amine (213 $\text{m}\mu$ in ether), whereas the frequency of typical enamines is shifted^{28, 30, 37} to 225–238 $\text{m}\mu$.



(9)

The formulation of enamines of quinuclidine in a mesomeric form would break Bredt's rule. No mesomerism occurs in 2,3-benzoquinuclidine between the nitrogen atom and the aromatic ring; thus, the compound does not exhibit the characteristic ultraviolet absorption of aromatic amines.⁴³ Dehydroquinuclidine may only be formulated as 1-azabicyclo[2.2.2]oct-2-ene; the overlap of the olefinic π -orbital and the lone pair orbital on nitrogen is precluded. Its ultraviolet spectrum exhibits merely end-absorption; the compound is

⁴¹ V. Prelog and O. Häfliger, *Helv. Chim. Acta* **32**, 1851 (1949).

⁴² N. J. Leonard, D. F. Morrow, and M. T. Rogers, *J. Am. Chem. Soc.* **79**, 5476 (1957).

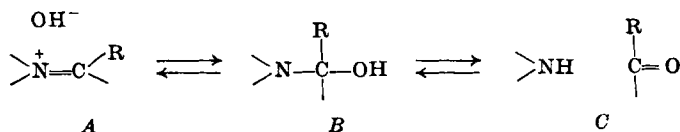
⁴³ B. M. Wepster, *Rec. Trav. Chim.* **71**, 1159 (1958).

resistant to hydrolysis but is hydrogenated readily, in contrast to other enamines.⁴⁴ Systematic measurements of the dissociation constants and ultraviolet spectra of various 3-aryldehydroquinuclidines and their comparison with the corresponding properties of saturated compounds have been used to separate the mesomeric and inductive effects of the substituents on the conjugated system.⁴⁵

Steric interactions of bulky substituents may also prevent the enamine system from assuming a planar arrangement. Unfortunately, no basicity and spectral data for such compounds have been reported. The course of reactions, e.g. of alkylation, of enamines obtained from pyrrolidine and 2-substituted cyclohexanones with a sufficiently bulky substituent could demonstrate decreased participation of the polarized mesomeric form.⁴⁶

3. The Problem of Pseudobases

The study of the enamine structure may be associated, to a certain degree, with the problem of the so-called pseudobases; an instructive, but somewhat specialized, review of these compounds was contributed by the late Professor Béke⁴⁷ to the first volume of this series. The name "pseudobases" was given by Hantzsch,⁴⁸ towards the end of the last century, to those α -aminocarbonols which undergo a structural change during salt formation and yield salts with the loss of one molecule of water. The liberation of pseudobases from their salts is accompanied by rehydration. This behavior has been observed with α,β -unsaturated heterocyclic compounds and, to a certain degree, with aromatic heterocyclic pyridine derivatives. As formulated by Gadamer,⁴⁹ the pseudobases represent a potential tautomeric system of three components, the quaternary hydroxide *A*, the carbinolamine *B*, and the open-chain amino-carbonyl derivative *C*, in which all three components exist in a mobile equilibrium:



⁴⁴ C. A. Grob, A. Kaiser, and E. Renk, *Helv. Chim. Acta* **40**, 2170 (1957).

⁴⁵ C. A. Grob, A. Kaiser, and E. Renk, *Chem. & Ind. (London)* p. 598 (1957).

⁴⁶ W. R. N. Williamson, *Tetrahedron* **3**, 314 (1958).

⁴⁷ D. Béke, *Advan. Heterocyclic Chem.* **1**, 167 (1963).

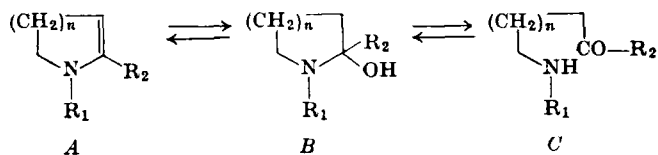
⁴⁸ A. Hantzsch, *Ber.* **32**, 575, 3109 (1899).

⁴⁹ J. Gadamer, *J. Prakt. Chem.* **84**, 817 (1911).

The experimental evidence for the existence of the corresponding tautomeric forms in solutions has been based on the study of their chemical reactivity and, to a lesser extent, on the study of tautomeric systems by means of physical methods. Not even an approximate quantitative evaluation can be presented by chemical experiments because of the different reaction rates of the individual tautomers; at best, they can be used as negative evidence, *viz.*, the absence of a certain tautomeric form in the reaction mixture can be assumed under the conditions used. The physico-chemical methods, due to low sensitivity, also did not give a satisfactory picture of the ratio of the corresponding tautomers.⁵⁰

According to Béke, the tautomeric three-component system postulated by Gadamer⁴⁹ has not been established yet for any compound. Rather, isolated tautomeric equilibria are valid between two forms under certain conditions and with a certain compound. The basicity of the pseudobase was considered by Béke to be the principal factor influencing the equilibrium. A detailed study of the available experimental material clearly shows, however, that basicity cannot be the only important factor. Stereochemical considerations, e.g. the ring size or the effective volume of substituents in the neighborhood of the nitrogen atom, must be taken into consideration.

The Gadamer system of three tautomeric components does not necessarily take for granted the simultaneous action of all three tautomeric equilibria, but rather it assumes two consecutive equilibria with the carbinolamine form (*B*) as an intermediate.



The existence of the third tautomer cannot be neglected in any case. The position of every equilibrium is determined by the combined effect of polar and steric structural factors as well as by the medium. As long as no equilibrium is too far from the common structural type, all three forms may be present simultaneously. Even if both equilibria are shifted to the limit in favor of forms *A* or *C*, the intermediate existence of the carbinolamine must be taken into account.

⁵⁰ N. J. Leonard and W. K. Musker, *J. Am. Chem. Soc.* **81**, 5631 (1959).

The cation of the quaternary ammonium hydroxide corresponds structurally to the polarized canonical form of the heterocyclic enamine. The non-polarized canonical form can be formally derived from the carbinolamine by dehydration. These relations point to a very close connection between enamines and pseudobases. For heterocyclic enamines, the existence of the corresponding carbinolamine or its acyclic tautomer, in addition to the dehydrated form, is possible under suitable conditions.⁵¹ Among these tautomeric forms, the position of equilibrium is usually determined by steric factors. Five-membered and six-membered ring compounds unsubstituted in position 2 generally exist in the cyclic form. The stability of the cyclic structure is reduced by substitution in that position. Lukeš *et al.* observed that partial ring-opening occurs with pyrroline³⁶ or piperidine derivatives^{38, 39} by the action of atmospheric moisture and leads to the formation of amino-ketones which can be detected by the ketonic carbonyl absorption at 1705–1710 cm^{-1} in the infrared spectra. For the analogs with eight- to twelve-membered (medium-sized) rings, where the cyclic tautomers are energetically disadvantageous, easier formation of acyclic ketones has been encountered. 1-Methyl-1-aza-2-cyclooctene, 1-methyl-1-aza-2-cyclononene, and 1-methyl-1-aza-2-cyclodecene with no substituents in position 2 react as amino-aldehydes.⁵⁰

The importance of ring size holds for the tautomerism of Δ^2 -pyrrol-5-ones and Δ^2 -dihydro-6-pyridones. Whilst the former compounds behave as cyclic 1-methyl-2-alkyl-2-hydroxy-5-pyrrolidones⁵² (or, on distillation, as dehydrated 1-methyl-2-alkyl- Δ^2 -pyrrolones), the latter compounds exist preferentially in the form of acyclic *N*-methanamides of δ -oxo-acids⁵³ (as shown by infrared spectroscopy); dehydration to Δ^2 -dihydro-6-pyridones is achieved only with difficulty.

4. Transannular Interactions

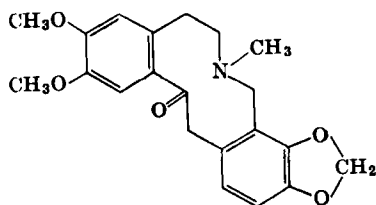
In this connection, transannular cyclization reactions between the ketonic carbonyl group and the amino nitrogen atom in medium-sized rings are of great interest. Cryptopine (10) is the most usual example, but not the best investigated case, of this kind. The appropriate inter-

⁵¹ A. Lipp and E. Widmann, *Ann. Chem.* **409**, 79 (1915).

⁵² R. Lukeš and Z. Linhartová, *Collection Czech. Chem. Commun.* **25**, 502 (1960).

⁵³ R. Lukeš, A. Fabryová, S. Doležal, and L. Novotný, *Collection Czech. Chem. Commun.* **25**, 1063 (1960).

actions on suitable azacyclanonones have been studied by Leonard *et al.*⁵⁴ using ultraviolet⁵⁵ and infrared⁵⁶ spectra and, in special cases, dipole moment and optical rotation dispersion data.⁵⁷ The transannular reaction corresponds^{55, 56} to the tautomeric equilibrium carbinolamine \rightleftharpoons amino-ketone.



(10)

1-Methyl-1-azacyclononan-5-ol-6-one⁵⁵ (**11**; R = Me) does not show a carbonyl absorption band at 264 m μ but only a weak maximum at 228 m μ , in contrast to the corresponding 2-hydroxynonanone (maxima at 217 and 264 m μ). Hence, no free carbonyl group is present under the conditions of measurement, and a dipolar structure (**12**; R = Me), obtained by a transannular interaction, must be postulated. An analogous absorption at 225–231 m μ has also been observed with enamines.

The occurrence of a transannular reaction depends primarily on the ring size of the starting azacyclanone and of the resulting bicyclic system. The driving force of the reaction can be seen in the tendency to bridge medium-sized rings, thus relieving non-bonding interactions and forming a conformationally favorable arrangement, usually corresponding to hydrindane or decalin. The analogous azacyclo-octanone and azacyclodecanone show behavior similar to that of the previous compound. Compounds with seven- and thirteen-membered rings do not show nitrogen-carbonyl transannular interactions: a distinct absorption band due to the carbonyl group appears in the spectra at the same frequency as for the homocyclic analogs.

A further factor influencing the transannular interaction is represented by the steric and electronic interaction of substituents on

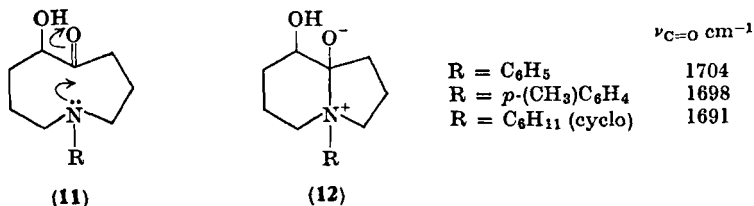
⁵⁴ N. J. Leonard, *Record Chem. Progr. (Kresge-Hooker Sci. Lib.)* **17**, 243 (1956).

⁵⁵ N. J. Leonard and M. Oki, *J. Am. Chem. Soc.* **77**, 6239 (1955).

⁵⁶ N. J. Leonard and M. Oki, *J. Am. Chem. Soc.* **77**, 6241 (1955).

⁵⁷ N. J. Leonard, J. A. Adamcik, C. Djerassi, and O. Halpern, *J. Am. Chem. Soc.* **80**, 4858 (1958).

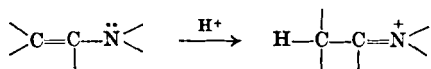
nitrogen. The presence of a bulky substituent in this position can change the spatial orientation of the lone pair orbital on the nitrogen atom so that the interaction is reduced. Thus, the extinction coefficient of the 228 $m\mu$ band of 1-*tert*-butyl-1-azacyclononan-5-ol-6-one⁵⁵ (**11**; R = *t*Bu) is considerably lower than that of the methyl analog. Similarly, an *N*-aryl substituent decreases⁵⁶ the interaction sterically and by the electron-withdrawing action of the aromatic residue. The carbonyl group absorption band in the infrared spectrum of an *N*-phenyl derivative occurs at almost the same position as does the band of an ordinary ketonic functional group. The interaction is strengthened again if electron-donor groups are introduced in the aromatic nucleus.



The steric effect is not dominant here, as proved by replacement of the phenyl group by a cyclohexyl residue.⁵⁶ *N*-Cyclopropyl-1-azacyclo-octan-5-one shows no transannular interaction due to the electronic influence.⁵⁸

B. STRUCTURE OF ENAMINE SALTS

In the formation of salts, addition of a proton occurs at the free electron pair of one of the mesomeric forms of the enamine. The salts are usually derived from the immonium structure. With tertiary enamines, there is a substantial difference between the free bases which possess a fixed vinylamine structure and their immonium salts.



In the infrared spectrum there is a marked shift (20–50 cm^{-1}) of the absorption maximum in the double-bond stretching region to higher

⁵⁸ N. J. Leonard and M. Oki, *J. Am. Chem. Soc.* **77**, 6245 (1955).

frequencies.^{58a} The shift is accompanied by an increased absorption intensity. This change is very characteristic of α,β -enamines (e.g. ethyl β -aminocrotonate,¹² 1-piperidino-2-ethyl-1-hexene,³ 3-pyrrolidino-3(2)-cholestene,³¹ etc.; see Table II), in contrast to the isomeric β,γ -unsaturated tertiary amines where protonation does not cause a band shift to occur in this spectral region.⁴¹ The ultraviolet absorption at 222–232.5 $m\mu$ corresponds to the immonium structure; only end absorption would be expected⁵⁸ if the structural change α,β -enamine \rightarrow α,β -unsaturated ammonium salt had occurred, because suppression of the interaction between the π -electrons of the double bond with the free electron pair on the nitrogen atom would result. No active hydrogen (Zerewitinov) was present in the salts, and no stretching or deformation vibrations of the nitrogen–hydrogen linkage were detected in the infrared spectra.^{3, 25}

Cases where the proton is localized on the nitrogen atom and an ammonium salt is formed are exceptional. Leonard¹ has reported a large participation of the ammonium salt in 1,4,4-trimethyl- Δ^2 -piperidine perchlorate and the occurrence of both of the forms with other piperidine derivatives. α,β -Unsaturated amines in which mesomerism is sterically prevented afford only the ammonium salt. Their spectrum in the C=C stretching-vibration region does not differ greatly from that of the free amine spectrum shown⁴¹ by neostrychnine and its perchlorate (in Nujol: neostrychnine, 1666 cm^{-1} ; neostrychnine perchlorate, 1665 cm^{-1} ; and strychnine, 1652 cm^{-1}).

With imines,¹⁷ salt formation is accompanied by two characteristic spectral changes: (a) a bathochromic shift in the ultraviolet region by as much as 50 $m\mu$, and (b) a high frequency shift of the $\text{—C}=\overset{+}{\underset{|}{\underset{|}{\text{N}}}}$ stretching vibration. The imine salts possess an active hydrogen, whereas their quaternization products¹⁸ exhibit the same spectral properties as the enamine salts.

For an immonium structure of the enamine salt, protonation of the polarized mesomeric form on the β -carbon atom is necessary. The behavior of dienamines shows^{59–61} that primary formation of an

^{58a} The shift depends little on the nature of the anion, whether it be inorganic (halide, perchlorate, or nitrate), complex (hexachlorostannate or hexachloroantimonate²⁵), or organic (picrate³⁵).

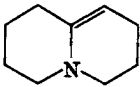
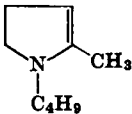
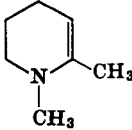
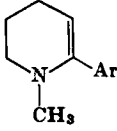
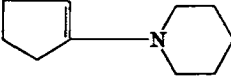
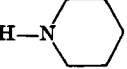
⁵⁹ G. Opitz and W. Merz, *Ann. Chem.* **652**, 139 (1962).

⁶⁰ G. Opitz and W. Merz, *Ann. Chem.* **652**, 163 (1962).

⁶¹ G. Opitz, M. Kleemann, and F. Zimmermann, *Angew. Chem.* **74**, 32 (1962).

TABLE II

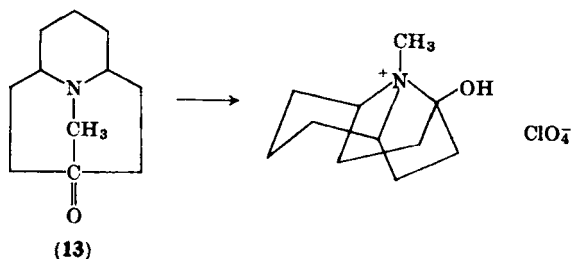
INFRARED SPECTRA OF SOME HETEROCYCLIC ENAMINES AND THEIR SALTS

| Compound | Base ν (C=C), cm^{-1} liquid film | Salt ν (C= $\overset{+}{\text{N}}^-$), cm^{-1} Nujol | Anion | Reference |
|---|--|--|--|-----------|
| | | | | |
| $\text{CH}_3-\underset{\text{NH}_2}{\text{C}}=\text{CH}-\text{COOC}_2\text{H}_5$ | 1625 | 1665 | Cl^- | 12 |
|  | 1652 | 1696 1680 | ClO_4^- I^- | 13 |
|  | 1639 | 1685 | ClO_4^- | 3 |
|  | 1650 | 1686 | ClO_4^- | 41 |
|  | 1630 | 1630 | picrate | 10 |
|  | 1623 | 1692 1670 | $\text{NO}_3^-^a$ $\text{SbCl}_6^-^a$ | 35 |
| $\text{C}_4\text{H}_9\text{C}(\text{C}_4\text{H}_9)=\text{CH}-\text{N}$  | 1656 | 1670 | $\text{SnCl}_6^-^a$ | 3 |

^a KBr disc.

ammonium salt, followed by the production of the immonium salt in the second step, cannot be excluded (see Section IV, A).

The salts of some enamines crystallize as hydrates. It is possible that these salts are actually derived from either the tautomeric carbinolamine or the amino-ketone forms. Steric factors should again be decisive. The salts obtained by an intramolecular cyclization of a bicyclic amino-ketone (**13**)⁵⁵ belong to the carbinolamine type; their infrared spectra reveal the presence of a hydroxyl group.



Schöpf *et al.*⁶² surprisingly observed that crystalline Δ^1 -tetrahydro-anabasine hydrobromide and hydrochloride show no absorption corresponding to the $\text{—C=N}^+\text{—}$, in contrast to the salt of the appropriate Δ^1 -piperideine. A molecule of water or methanol, which is present according to the analytical data, is evidently added across the $\text{—C=N}^+\text{—}$ double bond with the formation of a 2-hydroxy (or 2-methoxy)-3-(2-piperidyl)piperidine.

Enamines with medium-sized rings could well undergo hydrolytic ring fission in acid; however, some cyclic immonium salts of this type have been reported.¹⁴⁸

C. PHYSICAL AND CHEMICAL METHODS USED TO STUDY THE ENAMINE STRUCTURE

Application of physico-chemical methods is of considerable value for determining the actual structures of the compounds discussed. Only by using such methods was it possible to solve these problems successfully. Leonard and Hauck¹ determined reliable criteria for

⁶² C. Schöpf, F. Braun, H. Koop, and G. Werner, *Ann. Chem.* **658**, 156 (1962).

enamines, and now standard procedures are available for the detection of the enamine grouping. Examples of these procedures may be summarized as follows:

(i) *Infrared spectra* have universal application. Conversion of an α,β -unsaturated tertiary amine into the corresponding immonium salt is accompanied by a characteristic shift of the double bond stretching maximum to higher frequencies^{17, 63} and by a simultaneous increase in the intensity¹⁸ (see Table II). The new absorption maximum is ascribed⁶⁴ to the $\text{—C}=\overset{+}{\underset{\text{|}}{\underset{\text{|}}{\text{N}}}}\text{—}$ stretching frequency. This shift does not occur for α,β -unsaturated amines where a planar arrangement of the enamine grouping (see above) is not possible. In the latter case, salt formation leads to the appearance of N—H bands in the spectrum. The presence of other tautomeric forms (e.g. amino-ketones^{36, 38, 39} or carbinolamines⁵⁷) has been established by infrared spectroscopy.

(ii) *Raman spectra*^{27, 65} show shifts similar to those observed in the infrared spectra.

(iii) *Ultraviolet spectra* were most useful in the determination of structures of the free enamines. In contrast to saturated tertiary amines, the α,β -unsaturated analogs exhibit a shift of the absorption maximum towards longer wavelengths and show an increased band intensity^{1, 28} (see Table III). In isolated cases the shift may be masked by band overlap. The bathochromic and hyperchromic change is caused by the auxochromic lone pair on the nitrogen atom interacting with the double bond π -electrons.^{29, 30}

If this interaction is not possible, the shift does not occur.³⁷ The ultraviolet spectra have been studied in connection with the structure of aliphatic³ and cyclic enamines,^{1, 28, 37, 43} *cis-trans* isomerism about their double bond,²⁷ and the structures of enamines with additional functional groups.^{17, 20, 31, 32} Ultraviolet spectral data have been used also as a general method to determine the structure of alkaloids and in the study of some reaction mechanisms.

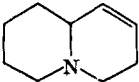
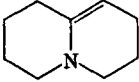
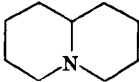
(iv) *Nuclear magnetic resonance* can differentiate between the possible tautomeric forms of imines^{9, 14, 15} (e.g. of γ -coniceine and myosmine). The olefinic proton of the β -carbon atom is not present in

⁶³ B. Witkop and J. B. Patrick, *J. Am. Chem. Soc.* **75**, 4474 (1953).

⁶⁴ O. E. Edwards, F. H. Clarke, and B. Douglas, *Can. J. Chem.* **32**, 235 (1954).

⁶⁵ K. W. F. Kohlrausch and A. Pongratz, *Ber.* **67**, 976 (1934); *Monatsh. Chem.* **70**, 226 (1937).

TABLE III
COMPARISON OF THE ULTRAVIOLET SPECTRAL DATA
FOR AN ENAMINE AND RELATED COMPOUNDS

| Compound | λ_{\max} , m μ | ϵ_{\max} |
|---|----------------------------|-------------------|
|  | 215 | 3100 |
|  | 228 | 5600 |
|  | 214 | 2800 |

spectra of compounds occurring in the imino form, in contrast to those of the corresponding tertiary enamines.¹⁵



(v) *Basicity.* Introduction of a double bond into the α,β -position of a primary or secondary amine always decreases the basicity, whereas with tertiary amines the same change increases the basicity.⁶⁶ A more distant double bond influences the basicity to a lesser degree. Table IV

TABLE IV
COMPARISON OF THE BASE STRENGTHS OF SOME SATURATED AND
UNSATURATED HETEROCYCLES

| Unsaturated compound | pK_a | pK_a of the corresponding saturated compound | ΔpK_a^a |
|--------------------------------------|--------|---|-----------------|
| 1,2-Dimethyl- Δ^2 -pyrroline | 11.94 | 10.26 | 1.68 |
| 1,2-Dimethyl- Δ^2 -piperidine | 11.43 | 10.26 | 1.17 |
| Δ^1 -Piperidine | 9.55 | 10.99 | -1.64 |
| 1-Methyl- Δ^3 -pyrroline | 9.92 | 10.36 | -0.44 |

^a $\Delta pK_a = pK_a$ (unsaturated) minus pK_a (saturated).

⁶⁶ D. F. Starr, H. Bulbrook, and R. M. Hixon, *J. Am. Chem. Soc.* **54**, 3971 (1932).

shows some illustrative examples taken from the work of Adams and Mahan.⁶⁷ Leonard and Hauck made similar measurements.¹ However, α,β -unsaturated amines with a non-planar arrangement show a pronounced decrease of basicity (see Section II, A) as compared with the saturated compound.

III. Preparation of Enamines

The pyrolysis of choline to *N,N*-dimethylvinylamine⁶⁸ was probably the first reported preparation of an enamine, but it is of historical interest only. A variety of methods for the preparation of enamines have been developed, and these compounds are now readily accessible.

A. PREPARATION OF ENAMINES BY CONDENSATION OF ALDEHYDES AND KETONES WITH AMINES

Condensation of aldehydes and ketones with secondary amines in the presence of dehydrating agents (often potassium carbonate⁶⁹⁻⁷¹) represents a general method of enamine preparation. By this procedure ketones afford the enamines directly, whereas aldehydes are converted in the first step into diamino derivatives which decompose on distillation to give the enamine and a molecule of the secondary amine. In the case of ketones and disubstituted acetaldehydes, the water formed by the reaction can be removed by azeotropic distillation with benzene, toluene, or xylene.^{27, 31, 72-75} In the case of derivatives of aromatic aldehydes, the formation of intermediary carbinolamines⁷⁶ is sometimes observed.

⁶⁷ R. Adams and J. E. Mahan, *J. Am. Chem. Soc.* **64**, 2588 (1942).

⁶⁸ K. H. Meyer and H. Hopf, *Ber.* **54**, 2274 (1921); J. v. Braun and G. Kirschbaum, *Ber.* **52**, 2261 (1919).

⁶⁹ C. Mannich and H. Davidsen, *Ber.* **69**, 2106 (1936).

⁷⁰ G. Opitz, H. Hellmann, and H. W. Schubert, *Ann. Chem.* **623**, 112 (1959).

⁷¹ R. Grewe, H. J. Arpe, and E. Petersen, *Ann. Chem.* **653**, 97 (1962).

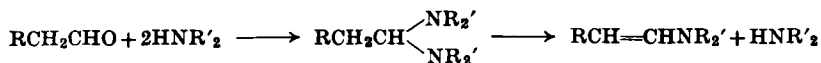
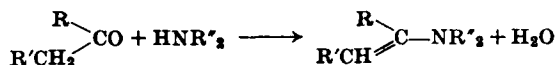
⁷² L. Birkofer and C. D. Barnikel, *Chem. Ber.* **91**, 1996 (1958).

⁷³ A. T. Blomquist and E. J. Moriconi, *J. Org. Chem.* **26**, 3761 (1961).

⁷⁴ G. Stork and J. W. Schulenberg, *J. Am. Chem. Soc.* **84**, 284 (1962).

⁷⁵ G. Stork, A. Brizzolara, H. K. Landesman, J. Szmuszkowicz, and R. Terrell, *J. Am. Chem. Soc.* **85**, 207 (1963).

⁷⁶ R. G. Kostianovskij and V. F. Bystrov, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk* 171 (1963); R. G. Kostianovskij and O. A. Panshin, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk* 182 (1963).



The preparation of enamines of aldehydes and especially of ketones has assumed a new importance since Stork's⁷⁵ observation in 1954 that their alkylation, acylation, or addition to α,β -unsaturated carbonyl compounds, followed by hydrolysis, leads to α -monosubstituted aldehydes or ketones. Pyrrolidine, piperidine, or morpholine is usually used as the secondary amine. The rate of enamine formation depends on the basicity of the secondary amine as well as on the steric environment of the carbonyl group of the aldehyde or ketone. The more basic pyrrolidine ($K = 1.3 \times 10^{-3}$) usually reacts more quickly than morpholine ($K = 2.44 \times 10^{-3}$). Although the basicity and steric requirements of the nitrogen atoms in pyrrolidine and piperidine ($K = 1.6 \times 10^{-3}$) are approximately equal, reactions with pyrrolidine are always faster. The difference is due to differing rates of dehydration of the primary products of the condensation of an aldehyde or ketone with the amine. In the transition state for this dehydration a trigonal carbon atom is part of a ring. By analogy with the solvolytic reactions of cyclopentane and cyclohexane derivatives, it is expected that reaction with the five-membered pyrrolidine ring will be faster than with the six-membered piperidine ring. Cyclic ketones generally react faster than aliphatic ketones and in the order: cyclopentanone > cyclohexanone > higher-membered cyclic ketones. Decreased reactivity indicates that the dehydration step determines the reaction rate. If the formation of carbinolamines were rate-determining, the reaction should be faster with cyclohexanone than with cyclopentanone.

In the preparation of enamines from α -substituted ketones, e.g. 2-alkylcyclohexanones, the less-substituted enamine is always formed because of steric interactions⁷⁷. This makes possible the introduction of a substituent on the α' -carbon atom of the ketones ($\text{R}_2\overset{\alpha}{\text{CH}}-\text{CO}-\overset{\alpha'}{\text{CH}}_2\text{R}$) via their enamines. Even 2-phenylcyclohexanone has been shown⁷⁸ to

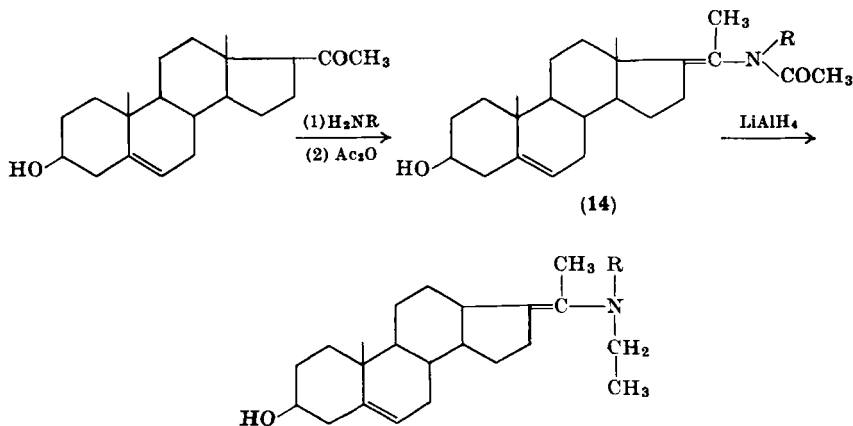
⁷⁷ E. J. Eisenbraun, J. Osiecki, and C. Djerassi, *J. Am. Chem. Soc.* **80**, 1261 (1958).

⁷⁸ M. E. Kuehne, *J. Am. Chem. Soc.* **81**, 5400 (1959).

give the less-substituted enamine on the basis of its ultraviolet spectrum. Apparently, formation of the enamine double bond towards the aryl substituent is favored somewhat by introduction of nitro groups onto the benzene ring.²³⁴ Alkylation of ketones via their anions affords, on the contrary, the most-substituted derivatives.⁷⁷

Enamines have been used for blocking steroidal ketones.^{32, 79-82} α,β -Unsaturated ketones afford dienamines.^{59, 82, 83}

Imines are formed by condensation of aldehydes or ketones with primary amines, but they form with more difficulty than enamines.^{84, 85} A special case of enamine preparation was described with 20-oxosteroids.⁸⁶ Treatment of these ketones with a primary amine gives a 20-ketimine, which is acetylated with acetic anhydride, with migration of the double bond and formation of 20-(*N*-acetylalkylamino)- $\Delta^{17(20)}$ -pregnene (**14**); reduction of **14** with lithium aluminum hydride affords the enamine.



⁷⁹ M. E. Herr and F. W. Heyl, *J. Am. Chem. Soc.* **74**, 3627 (1952).

⁸⁰ H. J. E. Loewenthal, *Tetrahedron* **6**, 293 (1959).

⁸¹ R. O. Clinton, A. J. Manson, F. W. Stonner, R. L. Clarke, K. F. Jennings, and P. E. Shaw, *J. Org. Chem.* **27**, 1148 (1962).

⁸² A. F. McKay, E. J. Tarlton, and C. Podesva, *J. Org. Chem.* **26**, 76 (1961).

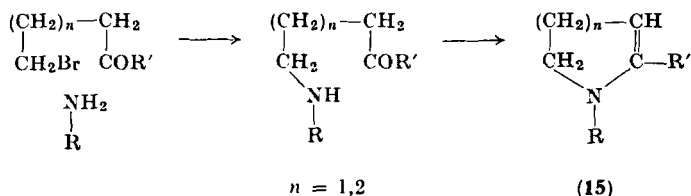
⁸³ S. Hünig and H. Kahane, *Chem. Ber.* **90**, 238 (1957).

⁸⁴ K. Löffler, *Ber.* **43**, 2035 (1910).

⁸⁵ K. N. Campbell, A. H. Sommers, and B. K. Campbell, *J. Am. Chem. Soc.* **66**, 82 (1944).

⁸⁶ W. Fritsch, J. Schmidt-Thomé, H. Ruschig, and W. Haede, *Chem. Ber.* **96**, 68 (1963).

If the amino group forms part of the ketone, as it does with γ -^{87, 88} and δ -amino-ketones,^{89, 90} heterocyclic enamines are obtained. 1,2-Dialkyl- Δ^2 -pyrrolines and 1,2-dialkyl- Δ^2 -piperideines (**15**) are formed from secondary amino groups, whereas primary amino groups⁹¹ lead to 2-alkyl- Δ^1 -pyrrolines and 2-alkyl- Δ^1 -piperideines. Gabriel⁹⁰ used the suitably substituted phthalimidoketone for the synthesis of the alkaloid γ -coniceine (**15**; R = H, R' = *n*-Pr, *n* = 2).



Salts of α -oxo- δ -aminovaleric acid and α -oxo- ϵ -aminocaproic acid^{92, 93} exist as such in the solid state, but in solution they are in equilibrium with the cyclic compounds, Δ^1 -pyrroline-2-carboxylic acid and Δ^1 -piperideine-2-carboxylic acid, respectively.⁹⁴

Instead of amino-ketones, compounds may be used which are capable of forming amino-ketones as intermediates. Thus, if phenols and phenol ethers are acylated with γ - or δ -amino acids in the presence of polyphosphoric acid, the intermediate amino-ketones cyclize to 2-aryl- Δ^1 -pyrrolines or 2-aryl- Δ^1 -piperideines⁹⁵ (Scheme 1).

The Hofmann degradation of β -benzoylpropionamide takes a similar course and leads to the formation of 2-phenyl- Δ^1 -pyrroline.⁹⁶

⁸⁷ J. B. Cloke, *J. Am. Chem. Soc.* **51**, 1174 (1929).

⁸⁸ A. Wohl, *Ber.* **34**, 1914 (1901).

⁸⁹ A. Lipp, *Ber.* **18**, 3284 (1895); **25**, 2190 (1892).

⁹⁰ S. Gabriel, *Ber.* **41**, 2010 (1908).

⁹¹ A. Haller and P. Ramart-Lucas, *Ann. Chim. (Paris)* [9] **8**, 5 (1917).

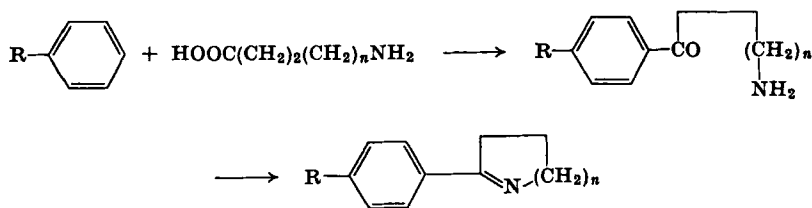
⁹² L. Macholán, *Naturwissenschaften* **46**, 357 (1959).

⁹³ L. Macholán, *Chem. Listy* **50**, 1818 (1956); *Collection Czech. Chem. Commun.* **22**, 479 (1957). L. Macholán and L. Skurský, *Chem. Listy* **49**, 1385 (1955). L. Skurský and L. Macholán, *Chem. Listy* **51**, 774 (1957); *Collection Czech. Chem. Commun.* **23**, 150 (1958).

⁹⁴ L. Macholán and E. Svátek, *Collection Czech. Chem. Commun.* **25**, 2564 (1960). L. Macholán, *Chem. Listy* **51**, 2122 (1957); *Collection Czech. Chem. Commun.* **24**, 550 (1959).

⁹⁵ W. Koller and P. Schlack, *Chem. Ber.* **96**, 93 (1963).

⁹⁶ A. P. Terent'ev, A. N. Kost, and A. M. Berlin, *Zh. Obshch. Khim.* **25**, 1613 (1955).

SCHEME 1. $R = OH, OCH_3$; $n = 1, 2$.

B. PREPARATION OF ENAMINES BY REDUCTION METHODS

The apparently simple procedures of partial dehydrogenation of pyrrolidines and partial hydrogenation of pyrroles afford Δ^1 -pyrrolines. However, the reaction is complex and is of little preparative value.⁹⁷⁻⁹⁹ Δ^1 -Pyrrolines may be obtained by isomerization of Δ^3 -pyrrolines.¹⁰⁰ From the preparative point of view, partial hydrogenation of quaternary pyridine salts in strongly alkaline media to give 1-alkyl- Δ^2 -piperideines is more important.¹⁰¹ Formation of heterocyclic enamines was observed in the reduction of *N*-methylpyrrolidone with lithium aluminum hydride,¹⁰² *N*-alkylpiperidones with sodium in ethanol,^{103, 104} and in the electrolytic reduction of *N*-methylglutarimide.¹⁰⁵

Δ^1 -Pyrrolines and Δ^1 -piperideines are also formed from γ -^{106, 107} and δ -nitrobutylalkylketones,¹⁰⁸⁻¹¹⁰ respectively, by catalytic hy-

⁹⁷ D. W. Fuhlhage and C. A. VanderWerf, *J. Am. Chem. Soc.* **80**, 6249 (1958).

⁹⁸ H. P. L. Gitels and J. P. Wibaut, *Rec. Trav. Chim.* **59**, 1091 (1940).

⁹⁹ J. P. Wibaut and W. Proost, *Rec. Trav. Chim.* **52**, 333 (1933).

¹⁰⁰ G. G. Evans, *J. Am. Chem. Soc.* **73**, 5230 (1951).

¹⁰¹ C. Schöpf, G. Herbert, R. Rausch, and G. Schröder, *Angew. Chem.* **69**, 391 (1957).

¹⁰² F. Galinovsky and R. Weiser, *Experientia* **6**, 377 (1950).

¹⁰³ R. Lukeš and J. Kovář, *Chem. Listy* **48**, 404 (1954); *Collection Czech. Chem. Commun.* **19**, 1215 (1954).

¹⁰⁴ L. Ruzicka, *Helv. Chim. Acta* **4**, 475 (1921).

¹⁰⁵ R. Lukeš and J. Kovář, *Chem. Listy* **48**, 692 (1954); *Collection Czech. Chem. Commun.* **19**, 1227 (1954). R. Lukeš and M. Smetáčková, *Collection Czech. Chem. Commun.* **5**, 61 (1931).

¹⁰⁶ M. L. Stein and A. Burger, *J. Am. Chem. Soc.* **79**, 154 (1957).

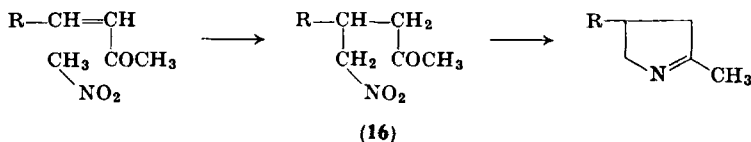
¹⁰⁷ M. C. Kloetzel, F. L. Chubb, and J. L. Pinkus, *J. Am. Chem. Soc.* **80**, 5773 (1958).

¹⁰⁸ J. Dhont and J. P. Wibaut, *Rec. Trav. Chim.* **63**, 81 (1944).

¹⁰⁹ E. Profft, F. Runge, and A. Jumar, *J. Prakt. Chem.* [4] **1**, 57 (1955).

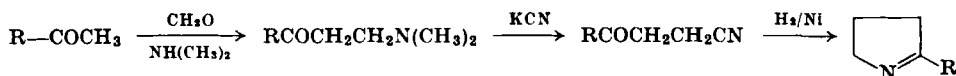
¹¹⁰ A. Sonn, *Ber.* **68**, 148 (1935); **72**, 2150 (1939).

drogenation over Raney nickel in ethanol or by treatment with zinc and hydrochloric acid (Scheme 2). γ -Nitro-ketones (**16**) are readily accessible by addition of nitromethane to α,β -unsaturated ketones.⁷ The intermediate Δ^1 -pyrroline *N*-oxides are sometimes isolated using zinc-ammonium chloride,^{111, 112} iron-sulfuric acid,¹⁰⁶ or hydrazine-Raney nickel¹¹³ as reducing reagents.



SCHEME 2

Δ^1 -Pyrrolines occur among the products of the hydrogenation of γ -keto-nitriles¹¹⁴⁻¹¹⁶ (Scheme 3) and the reduction of unsaturated ketoximes with zinc-acetic acid.¹¹⁷

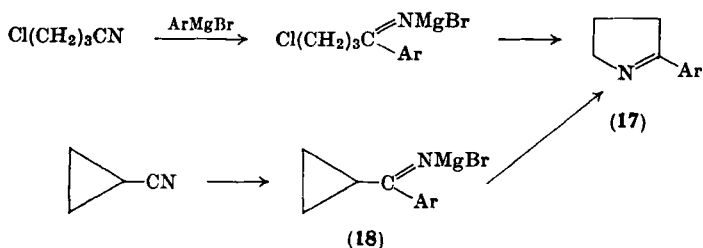


SCHEME 3

C. PREPARATION OF ENAMINES BY MEANS OF ORGANOMETALLIC REAGENTS

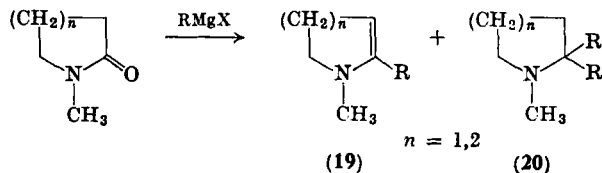
Δ^1 -Pyrrolines (17) and Δ^1 -piperideines are formed on treatment of γ -^{66, 118–120} and δ -halogenonitriles, ^{121, 122} respectively, with Grignard

- 111 R. Bonnett, R. F. C. Brown, V. M. Clark, I. O. Sutherland, and A. Todd, *J. Chem. Soc.* 2094 (1959).
- 112 R. F. C. Brown, V. M. Clark, and A. Todd, *Proc. Chem. Soc. (London)* 97 (1957).
- 113 M. C. Kloetzel, F. L. Chubb, R. Gobran, and J. L. Pinkus, *J. Am. Chem. Soc.* **83**, 1128 (1961).
- 114 J. H. Burrehalter and J. H. Short, *J. Org. Chem.* **23**, 1281 (1958).
- 115 E. B. Knott, *J. Chem. Soc.* 186 (1948).
- 116 H. Ruppe and F. Gisiger, *Helv. Chim. Acta* **8**, 338 (1925).
- 117 R. Griot and T. Wagner-Jauregg, *Helv. Chim. Acta* **42**, 121 (1959).
- 118 L. C. Craig, H. Bulbrook, and R. M. Hixon, *J. Am. Chem. Soc.* **53**, 1831 (1931).
- 119 J. B. Cloke, *J. Am. Chem. Soc.* **51**, 1174 (1929); P. Lipp and H. Seeles, *Ber.* **62**, 2456 (1929).
- 120 J. B. Cloke, E. Stehr, T. R. Steadman, and L. C. Westcott, *J. Am. Chem. Soc.* **67**, 1587 (1945).
- 121 J. B. Cloke and O. Ayers, *J. Am. Chem. Soc.* **56**, 2144 (1934).
- 122 R. Salathiel, J. M. Burch, and R. M. Hixon, *J. Am. Chem. Soc.* **59**, 5361 (1937).



reagents. The resulting ketimine reacts with the halogen atom to form the desired enamine: no hydrolysis occurs on working up the reaction mixture. The pyrrolines probably form mainly by a direct thermal displacement of the chloroimine and not by rearrangement of a possible cyclopropylketimine intermediate (18). Since the latter compound is one of the by-products, a small amount of the pyrroline may be formed by the second route. The cyclopropylketimine is presumably formed by the Grignard reagent reacting with the cyclopropyl cyanide, which is formed by cyclization of γ -chlorobutyronitrile under the influence of the organomagnesium halide acting as a base. It has been established that the ketimines obtained from a Grignard reagent and cyanocyclopropanes are thermally isomerized to pyrrolines.^{123, 124} In an analogous manner, the more reactive benzylmagnesium chloride affords 2,2-dibenzylpyrrolidine.¹¹⁴

The reaction of Grignard reagents with *N*-methyl lactams has been studied by Lukeš *et al.* With the five- and six-membered rings, 2,2-dialkylated bases (20) are formed as by-products in addition to the expected 1-methyl-2-alkylpyrrolines¹²⁵⁻¹²⁸ and 1-methyl-2-alkyl-



¹²³ J. B. Cloke, L. H. Baer, J. M. Robbins, and G. E. Smith, *J. Am. Chem. Soc.* **67**, 2155 (1945).

¹²⁴ J. V. Murray and J. B. Cloke, *J. Am. Chem. Soc.* **68**, 126 (1946).

¹²⁵ R. Lukeš, *Collection Czech. Chem. Commun.* **2**, 531 (1931); *Chem. Listy* **27**, 121 (1933).

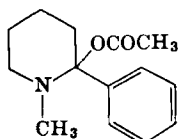
¹²⁶ L. C. Craig, *J. Am. Chem. Soc.* **55**, 295 (1933).

¹²⁷ R. Lukeš and Z. Veselý, *Collection Czech. Chem. Commun.* **24**, 944 (1959); *Chem. Listy* **52**, 1299 (1958).

¹²⁸ R. Lukeš and O. Červinka, *Collection Czech. Chem. Commun.* **26**, 1893 (1961).

piperideines¹²⁹⁻¹³³ (19), respectively. Aromatic Grignard reagents afford only the unsaturated bases, probably because of steric factors. The reaction has been carried out with non-methylated¹³⁴ and also with variously substituted lactams.^{135, 136} Polycyclic compounds containing the piperidone system add only one molecule of the Grignard reagent, probably due to steric hindrance.^{137, 138}

Treatment of 1-methyl-2-piperidone with phenylmagnesium bromide and subsequent reaction with acetic anhydride and then water gave the acetate **21** in small yield.¹³⁹ This indicates that the salt of the carbinolamine form is an intermediate which, on liberation, affords the cyclic enamine in the five- and six-membered series, for steric reasons.



(21)

From a preparative point of view, Lukeš's¹⁴⁰ observation that the perchlorates of pyrrolines and piperideines and the picrates of 2,2-disubstituted saturated bases crystallize well is important, for these types of bases may thus be isolated. Some authors who repeated the experiments of Lukeš did not isolate both types, probably because of

¹²⁹ R. Lukeš and O. Grossmann, *Collection Czech. Chem. Commun.* **8**, 533 (1936).

¹³⁰ R. Lukeš and M. Smetáčková, *Collection Czech. Chem. Commun.* **6**, 231 (1934); *Chem. Listy* **29**, 316, 334 (1935).

¹³¹ R. Lukeš, *Collection Czech. Chem. Commun.* **4**, 181 (1932).

¹³² R. Lukeš and F. Šorm, *Chem. Listy* **36**, 282 (1942); *Collection Czech. Chem. Commun.* **12**, 356 (1947).

¹³³ R. Lukeš and Z. Veselý, *Collection Czech. Chem. Commun.* **24**, 2318 (1959); *Chem. Listy* **52**, 1608 (1958).

¹³⁴ R. Lukeš, F. Šorm, and Z. Arnold, *Collection Czech. Chem. Commun.* **12**, 641 (1947); *Chem. Listy* **41**, 250 (1947).

¹³⁵ R. Lukeš and V. Dědek, *Chem. Listy* **51**, 2074 (1957); *Collection Czech. Chem. Commun.* **24**, 391 (1959).

¹³⁶ R. Lukeš and M. Večeřa, *Collection Czech. Chem. Commun.* **19**, 263 (1954); *Chem. Listy* **47**, 541 (1953).

¹³⁷ K. Winterfeld and E. Hoffmann, *Arch. Pharm.* **275**, 5, 526 (1937).

¹³⁸ K. Winterfeld and P. Petkow, *Chem. Ber.* **82**, 156 (1949).

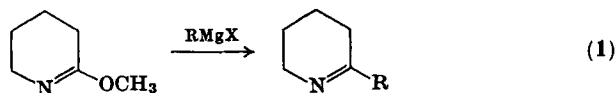
¹³⁹ J. Lee, A. Ziering, S. D. Heineman, and L. Berger, *J. Org. Chem.* **12**, 885 (1947).

¹⁴⁰ R. Lukeš, *Bull. International Acad. Sci. Boheme* p. 1 (1930).

unsuitable isolation techniques; either pyrrolines^{67, 141} or saturated 2,2-dialkylated bases¹⁴² were reported as the sole products.

Lactams with larger rings, e.g. seven-,^{143, 144} eight-,¹⁴⁵ nine-,¹⁴⁶ eleven-, and thirteen-membered lactams,¹⁴⁷ yield acyclic amino-ketones as the sole products, as is to be expected. With the seven- and thirteen-membered rings, the existence of both forms might be expected, and the salts of 1-methyl-2- α -naphthyl-1-aza-2-cycloheptene and 1-methyl-2- α -naphthyl-1-aza-2-cyclotridecene have been prepared in both the cyclic enamine and the acyclic amino-ketone forms.¹⁴⁸ The structure of the products also depends upon the Grignard reagent used.

2-Alkyl- Δ^1 -piperidineines and 2-alkyl-1-aza-1-cycloheptenes are formed in good yields on treatment of imino-ethers with a Grignard reagent^{149, 150} (Eq. 1).



Reactions with the cyclic imides of dicarboxylic acids (dioxopyrrolizidine¹⁵¹ and *N*-methylsuccinimide) furnish 1-methyl-2-alkyl-5-pyrrolinones,^{152, 153} which are also accessible from levulinic acid and

¹⁴¹ L. C. Craig, *J. Am. Chem. Soc.* **55**, 2543 (1933).

¹⁴² R. Adams and E. F. Rogers, *J. Am. Chem. Soc.* **63**, 228 (1941).

¹⁴³ R. Lukeš and K. Smolek, *Collection Czech. Chem. Commun.* **11**, 506 (1939).

¹⁴⁴ R. Lukeš, V. Dudek, O. Sedláková, and I. Kořán, *Collection Czech. Chem. Commun.* **26**, 1105 (1961).

¹⁴⁵ R. Lukeš and J. Dobáš, *Collection Czech. Chem. Commun.* **15**, 303 (1950).

¹⁴⁶ R. Lukeš and J. Málek, *Collection Czech. Chem. Commun.* **16**, 23 (1951); *Chem. Listy* **45**, 72 (1951).

¹⁴⁷ R. Lukeš and L. Karlíčková, *Collection Czech. Chem. Commun.* **26**, 2245 (1961).

¹⁴⁸ O. Červinka and L. Hub, *Collection Czech. Chem. Commun.* **30**, 3111 (1965).

¹⁴⁹ R. Lukeš and O. Červinka, *Chem. Listy* **52**, 83 (1958); *Collection Czech. Chem. Commun.* **24**, 1846 (1959).

¹⁵⁰ O. Červinka, *Collection Czech. Chem. Commun.* **24**, 1146 (1959); *Chem. Listy* **52**, 1145 (1958).

¹⁵¹ F. Micheel and W. Flitsch, *Chem. Ber.* **94**, 1749 (1961).

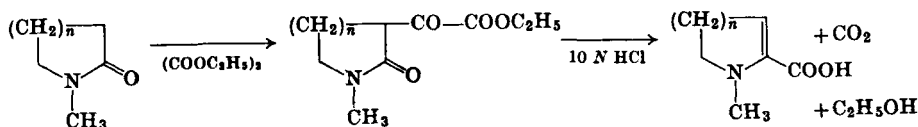
¹⁵² R. Lukeš and K. Smolek, *Collection Czech. Chem. Commun.* **7**, 476 (1935); *Chem. Listy* **30**, 185 (1936).

¹⁵³ R. Lukeš and M. Černý, *Collection Czech. Chem. Commun.* **23**, 497 (1958); *Chem. Listy* **51**, 1327 (1957).

primary amines.¹⁵⁴ An analogous Reformatski reaction with *N*-methylsuccinimide has also been described.¹⁵⁵ Reaction with *N*-methylglutarimide leads, in contrast to non-cyclic δ -oxocarboxamides which are dehydrated, to 1-methyl-2-alkyl-4,5-dihydro-6-pyridones on distillation.^{156, 157}

D. PREPARATION OF ENAMINES BY MEANS OF THE CLAISEN CONDENSATION

The reactivity of the α -methylene group in lactams allows Claisen condensation with esters of formic, oxalic, and arylcarboxylic acids. Treatment of ethyl formate with *N*-methylpiperidone, followed by acidification, yields a salt of 1-methyl- Δ^2 -piperideine, whereas in an alkaline medium its dimer was isolated.^{34, 158} With oxalic acid ester as the condensing reagent, 1-methyl- Δ^2 -pyrroline-2-carboxylic acid¹⁵⁹ and 1-methyl- Δ^2 -piperideine-2-carboxylic acid¹⁶⁰ were obtained (Scheme 4).



SCHEME 4. $n = 1, 2$

Pyrrolidone (**22**) and piperidone themselves afford Δ^1 -pyrroline-2-carboxylic acid¹⁶¹ (**23**) and Δ^1 -piperideine-2-carboxylic acid.¹⁶²

1-Methyl-3-aryl-2-pyrrolidones and 1-methyl-3-aryl-2-piperidones are cleaved by the action of concentrated hydrochloric acid to

¹⁵⁴ R. Lukeš and V. Prelog, *Chem. Listy* **24**, 251 (1930); *Collection Czech. Chem. Commun.* **1**, 282 (1929).

¹⁵⁵ R. Lukeš and F. Šorm, *Collection Czech. Chem. Commun.* **12**, 637 (1947); R. Lukeš and D. Pařízková, *Collection Czech. Chem. Commun.* **15**, 156 (1950).

¹⁵⁶ R. Lukeš and J. Gorocholinskij, *Collection Czech. Chem. Commun.* **8**, 223 (1936).

¹⁵⁷ R. Lukeš and M. Černý, *Chem. Listy* **51**, 1862 (1957); *Collection Czech. Chem. Commun.* **23**, 946 (1958).

¹⁵⁸ C. Schöpf and H. L. De Wall, *Chem. Ber.* **89**, 915 (1956).

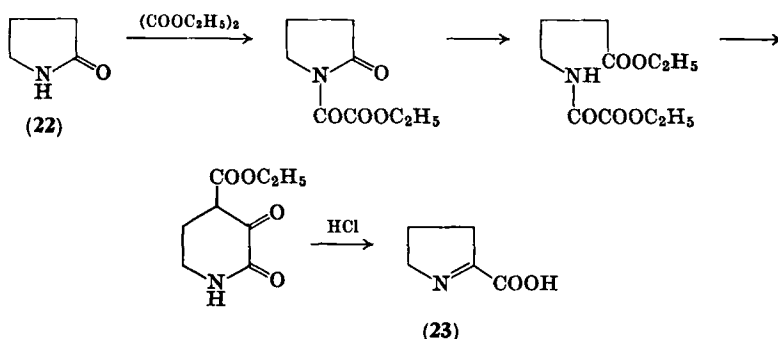
¹⁵⁹ K. H. Büchel and F. Korte, *Chem. Ber.* **97**, 2453 (1962).

¹⁶⁰ F. Korte, K. H. Büchel, H. Mäder, G. Römer, and H. H. Schulze, *Chem. Ber.* **95**, 2424 (1962).

¹⁶¹ K. Hasse and A. Wieland, *Chem. Ber.* **93**, 1686 (1960).

¹⁶² K. Langheld, *Ber.* **42**, 392 (1909).

1-methyl-2-aryl- Δ^2 -pyrrolines¹⁶³ and 1-methyl-2-aryl- Δ^2 -piperideines,¹⁶⁴ respectively. The *N*-acyl lactams furnish 2-substituted Δ^1 -pyrrolines on hydrolysis.¹⁶⁵



E. PREPARATION OF ENAMINES BY ELIMINATION REACTIONS

Δ^1 -Pyrroline has been prepared in low yield by oxidation of proline with sodium hypochlorite,¹⁶² persulfate,¹⁶⁶ and periodate.¹⁶⁷ The best procedure for the preparation of Δ^1 -pyrroline and Δ^1 -piperideine consists of dehydrohalogenation of *N*-chloropyrrolidine and *N*-chloropiperidine, which are readily accessible by chlorination with *tert*-butyl hypochlorite.¹⁶⁸ Δ^1 -Pyrroline and Δ^1 -piperideine are products of enzymic oxidative deamination of putrescine and cadaverine, or ornithine and lysine, respectively.^{169, 170} This process plays an important part in metabolism and in the biosynthesis of various heterocyclic compounds, e.g. alkaloids.

Another convenient method for the preparation of enamines involves the dehydrogenation of saturated bases with mercuric acetate. A *trans*-1,2-elimination probably occurs. The electron pair on the nitrogen atom and the hydrogen atom to be eliminated must both be axial. Thus, for example, yohimbine (24) can be dehydrogenated by mercuric acetate, whereas reserpine (25) or pseudoyohimbine (26) do

¹⁶³ F. Korte and H. J. Schulze-Steinen, *Chem. Ber.* **95**, 2444 (1962).

¹⁶⁴ E. Späth and H. Bretschneider, *Ber.* **61**, 327 (1928).

¹⁶⁵ E. Späth, J. P. Wibaut, and F. Kesztlér, *Ber.* **71**, 100 (1938).

¹⁶⁶ K. Lang, *Z. Physiol. Chem.* **241**, 68 (1936).

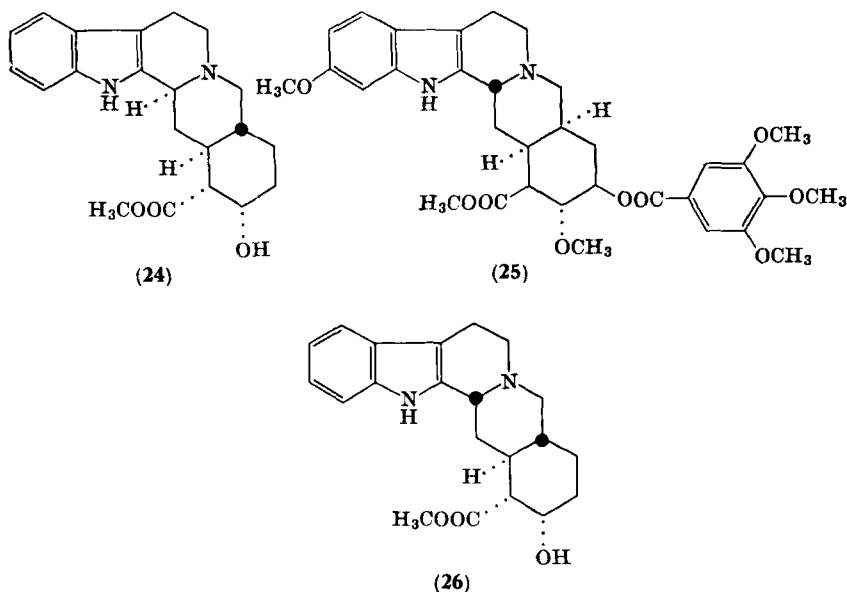
¹⁶⁷ L. Skurský, *Z. Naturforsch.* **14b**, 473 (1959).

¹⁶⁸ C. Schöpf, *Angew. Chem.* **59**, 174 (1947).

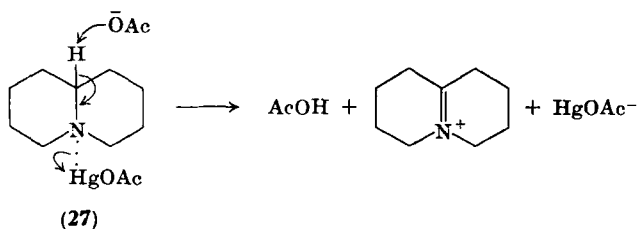
¹⁶⁹ P. J. G. Mann and W. R. Smithies, *Biochem. J.* **61**, 89 (1955).

¹⁷⁰ W. B. Jacoby and J. Fredericks, *J. Biol. Chem.* **234**, 2145 (1959).

not react.¹⁷¹ Localization of the double bond formed follows the Saytzeff rule.



Mercuric acetate and a tertiary base in 5% aqueous acetic acid¹⁷² yield a mercurated complex, which subsequently forms mercurous acetate and acetic acid. In this manner, quinolizidine (27) and its derivatives,¹⁷³ 1-azabicyclo[4.3.0]nonane, 1-azabicyclo[5.3.0]-



¹⁷¹ F. L. Weisenborn and P. A. Diassi, *J. Am. Chem. Soc.* **78**, 2023 (1956).

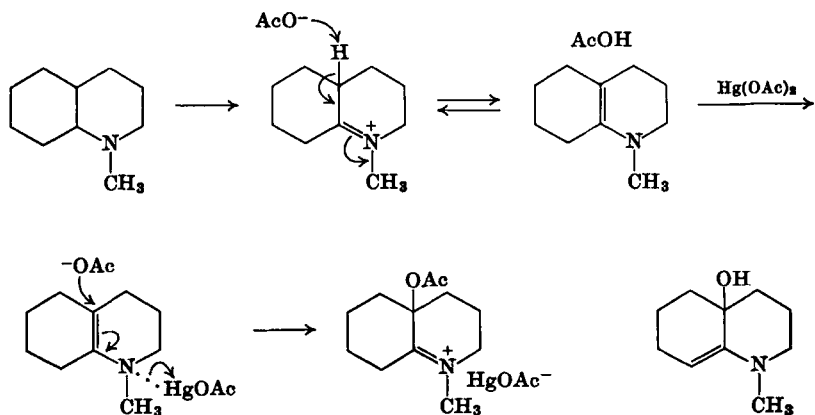
¹⁷² N. J. Leonard, A. S. Hay, R. W. Fulmer, and V. W. Gash, *J. Am. Chem. Soc.* **77**, 439 (1955).

¹⁷³ N. J. Leonard, R. W. Fulmer, and A. S. Hay, *J. Am. Chem. Soc.* **78**, 3457 (1956).

decane, 1-azabicyclo[5.4.0]undecane, and 1-azabicyclo[5.5.0]-dodecane,¹⁷⁴ have been oxidized.

The 1,2-, 1,2,5-, 1,3,4-, and 1,2,2,5-substituted pyrrolidines afford the corresponding pyrrolines very readily. In the case of 1,2,3-trimethylpyrrolidine, the formation of a double bond involving the unsubstituted α -carbon atom is followed by dimerization of the intermediate to 1,5,5-trimethyl-3-(1,5,5-trimethyl-2-pyrrolidyl)- Δ^2 -pyrroline.¹⁷⁵ The formation of oligomers is a frequent complication in the preparation of heterocyclic enamines. On dehydrogenation of 1-methylpyrrolidine, a dimer or trimer is obtained.¹⁷⁵ In addition to other products, the same dimer is formed in the reduction of *N*-methylpyrrole with zinc and hydrochloric acid.¹⁷⁶ Dehydrogenation of 1,3-dimethylpyrrolidine affords the dimer. Dehydrogenation of 1,3,4-trimethylpyrrolidine, followed by dimerization and oxidation, gives 2-(1,3,4-trimethyl-2-pyrrolidyl)pyrrole.

In the dehydrogenation of *cis*- and *trans*-1-methyldecahydroquinolines, hydroxylation takes place by the following mechanism:¹⁷⁷



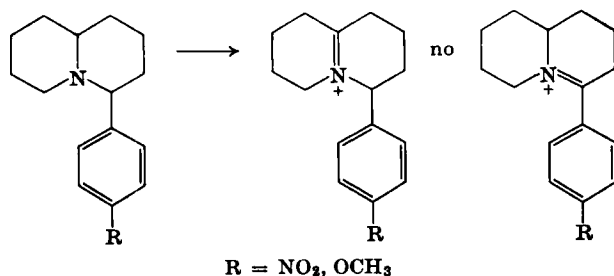
¹⁷⁴ N. J. Leonard, W. J. Middleton, P. D. Thomas, and D. Choudhury, *J. Org. Chem.* **21**, 344 (1956).

¹⁷⁵ N. J. Leonard and A. G. Cook, *J. Am. Chem. Soc.* **81**, 5627 (1959).

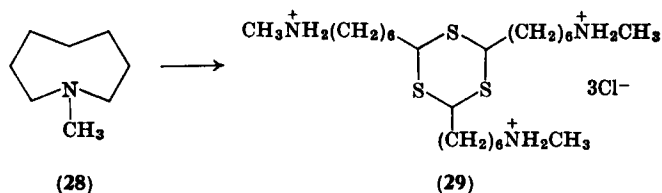
¹⁷⁶ R. Lukeš, J. Plešek, and J. Trojánek, *Collection Czech. Chem. Commun.* **24**, 1987 (1959).

¹⁷⁷ N. J. Leonard, L. A. Miller, and P. D. Thomas, *J. Am. Chem. Soc.* **78**, 3463 (1956).

The possibility of forming an enamine by dehydrogenation of a saturated base can be determined by a test due to Bohlmann¹⁷⁸⁻¹⁸⁰: piperidine derivatives possessing at least two axial carbon-hydrogen bonds in a position *trans* to the free electron pair on the nitrogen atom exhibit a characteristic infrared absorption between 2700–2800 cm^{-1} . Compounds which do not fulfil this condition cannot usually be dehydrogenated with mercuric acetate.¹⁸¹ Consequently, the 4-arylated quinolizidines are dehydrogenated merely to the 9,10-dehydro-compounds.^{181a}



Dehydrogenation of 1-methyl-1-azacyclooctane (28) with mercuric acetate, followed by treatment with hydrogen sulfide and hydrochloric acid, gave the hydrochloride of 2,4,6-tris-(6-methylamino-hexyl)trithiane (29) only.⁴⁸ Analogous compounds have been obtained



also in the dehydrogenation of 1-methyl-1-azacyclononane and 1-methyl-1-azacycloheptane. These results give further evidence about the instability of enamines with medium-sized rings.

¹⁷⁸ F. Bohlmann, *Angew. Chem.* **69**, 641 (1957).

¹⁷⁹ F. Bohlmann, W. Weise, H. Sander, H. G. Hanke, and E. Winterfeld, *Chem. Ber.* **90**, 653 (1957).

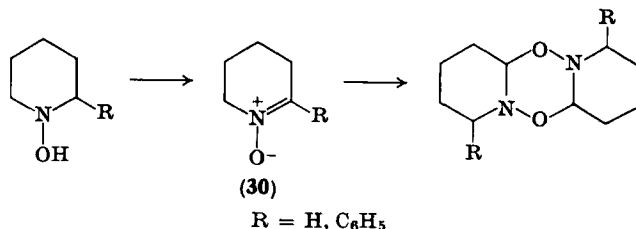
¹⁸⁰ F. Bohlmann, W. Weise, D. Rahtz, and C. Arndt, *Chem. Ber.* **90**, 2176 (1958).

¹⁸¹ N. J. Leonard and D. F. Morrow, *J. Am. Chem. Soc.* **80**, 371 (1958).

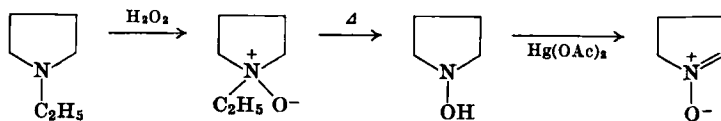
^{181a} F. Bohlmann and P. Strehle, *Tetrahedron Letters* No. 3, 167 (1965).

If other groups are present in the base subjected to the dehydrogenation, subsequent reactions can take place. Thus, dehydrogenation of amino-alcohols leads to aza-oxa compounds.^{182, 183}

Oxidation of *N*-hydroxypiperidine with cupric acetate or potassium ferricyanide gives Δ^1 -piperidine 1-oxide (**30**) in addition to a dimer or trimer.^{184, 185} Dehydrogenation of 1-hydroxy-2-phenylpiperidine takes a similar course.¹⁸⁶



1-Ethylpyrrolidine 1-oxide (obtained by oxidation of 1-ethylpyrrolidine with hydrogen peroxide) decomposes at elevated temperatures with the formation of ethylene and *N*-hydroxypyrrolidine which, in turn, may be oxidized to Δ^1 -pyrroline 1-oxide¹⁸⁷ (Scheme 5).



SCHEME 5

F. PREPARATION OF ENAMINES BY SOME SPECIAL METHODS

An interesting formation of a cyclic imine with a three-membered ring (**31**) was encountered in the pyrolysis of azidostyrene.¹⁸⁸ Compounds of this type are also considered as intermediates in the Neber rearrangement of tosyloxyimino-ketones.

¹⁸² N. J. Leonard and W. K. Musker, *J. Am. Chem. Soc.* **82**, 5148 (1960).

¹⁸³ W. Schneider and H. Götz, *Ann. Chem.* **653**, 85 (1962).

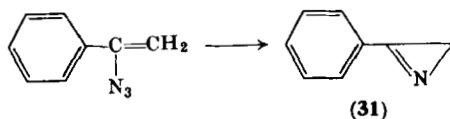
¹⁸⁴ J. Thesing and H. Meyer, *Chem. Ber.* **89**, 2159 (1956).

¹⁸⁵ J. Thesing and H. Meyer, *Ann. Chem.* **609**, 46 (1957).

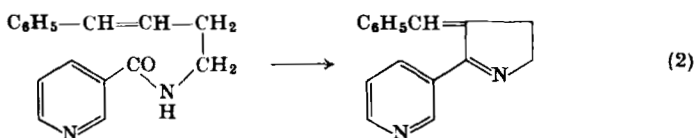
¹⁸⁶ J. Thesing and W. Sirrenberg, *Chem. Ber.* **91**, 1978 (1958).

¹⁸⁷ J. Thesing and W. Sirrenberg, *Chem. Ber.* **92**, 1748 (1959).

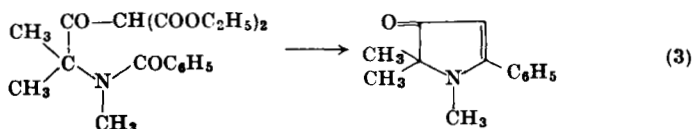
¹⁸⁸ G. Smolinsky, *J. Am. Chem. Soc.* **83**, 4483 (1961).



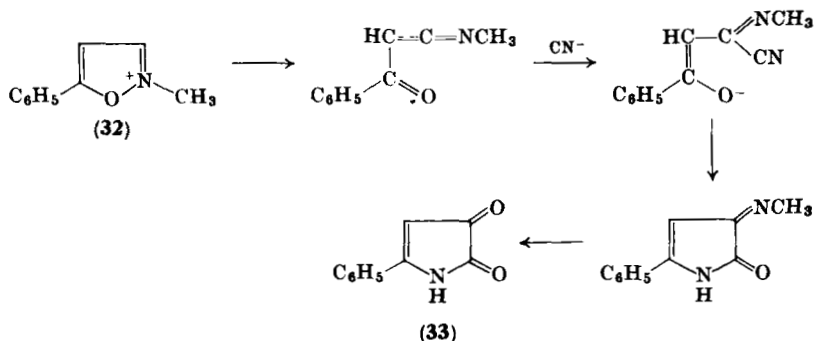
The synthesis (Eq. 2) of a Δ^1 -pyrroline was achieved by a procedure^{189, 190} similar to the Bischler-Napieralski preparation of 3,4-dihydroisoquinolines from *N*-acyl phenethylamines.



Esters of acylated aminoisobutyrylmalonic acids are easily converted into 3-oxo- Δ^2 -pyrrolines^{191, 192} (Eq. 3).



4,5-Dioxo- Δ^2 -pyrrolines (**33**) have been obtained from isoxazolum salts (**32**) by the action of alkali cyanides followed by ring-opening and reclosure.¹⁹³



¹⁸⁹ S. Sugasawa and S. Ushioda, *Tetrahedron* **5**, 48 (1959).

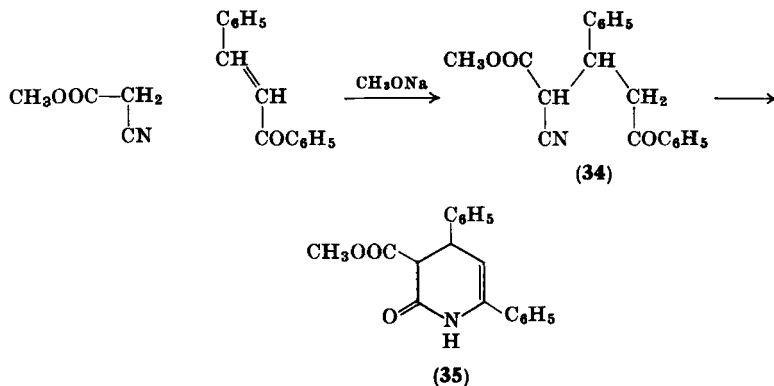
¹⁹⁰ T. Mizoguchi, *Chem. Pharm. Bull. (Tokyo)* **9**, 818 (1961).

¹⁹¹ S. Gabriel, *Ber.* **46**, 1358 (1913).

¹⁹² E. Immendörfer, *Ber.* **48**, 612 (1915).

¹⁹³ O. Mumm and H. Münchmeyer, *Ber.* **43**, 3345 (1910); O. Mumm and H. Hornhardt, *Ber.* **70**, 1930 (1937).

Condensation of ethyl cyanoacetate, cyanoacetamide, or malononitrile with α,β -unsaturated ketones leads to δ -oxonitriles (34) from which, in turn, dihydropyridones (35) may be obtained.¹⁹⁴



IV. Reactions of Enamines

The conjugated double bond of enamines readily undergoes many reactions. The reactions of imines with a double bond between the nitrogen and carbon atoms are also discussed to allow comparison. Some reactions of heterocyclic compounds containing the enamine grouping as a part of the aromatic ring are also considered. The reactions of these compounds can be divided on a mechanistic basis into three groups:

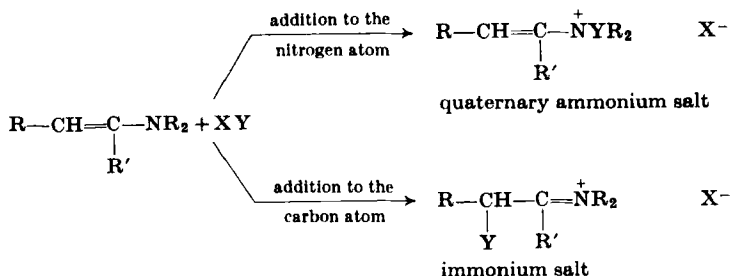
- A. Reactions of electrophilic reagents with the double bond of enamines.
- B. Reactions of enamine salts with nucleophilic reagents.
- C. Aldolization reactions of enamines (a special case combining classes A and B).

A. REACTIONS OF ELECTROPHILIC REAGENTS WITH THE DOUBLE BOND OF ENAMINES

With the non-polarized mesomeric form of an enamine, the electrophile should add to the nitrogen atom forming an ammonium salt, whereas with compounds reacting in the polarized mesomeric form,

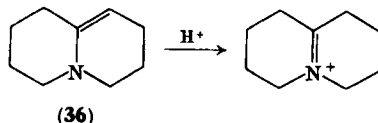
¹⁹⁴ E. P. Kohler, A. Graustein, and D. R. Merrill, *J. Am. Chem. Soc.* **44**, 2536 (1922).

addition takes place at the β -carbon atom and immonium salts are formed.

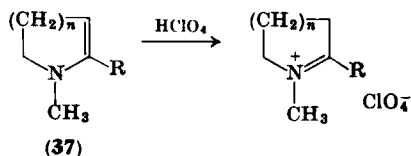


1. Addition of a Proton: Salt Formation^{194a}

On treatment with acids the enamines undergo a structural change (as stated above, e.g. in Section II, B) provided conjugation of the double bond between the carbon atoms with the electron pair on the nitrogen atom is not precluded by steric or other factors.^{37, 44} Thus $\Delta^{1(9)}$ -dehydroquinolizidine (36) and some more complicated compounds containing this system form immonium salts. Also the salts of



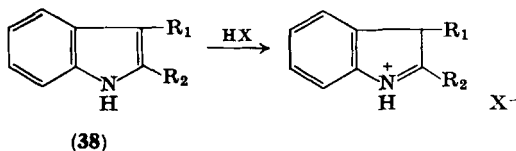
1-methyl-2-alkyl- Δ^2 -pyrrolines and 1-methyl-2-alkyl- Δ^2 -piperideines (37), prepared by Lukeš *et al.*, possess a double bond in the Δ^1 -position. Similarly, the salts of aliphatic enamines obtained on treatment of aldehydes or ketones with secondary amines possess the immonium structure.^{3, 195}



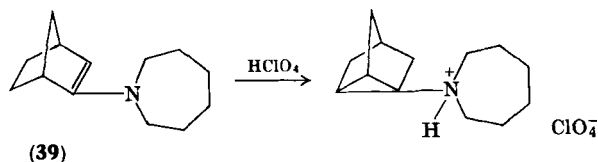
^{194a} In most cases, perchlorates are used for the characterization of enamines because of good crystallization properties and the small nucleophilicity of the perchlorate ion. Hexachlorostannates,²⁵ hexachloroantimonates,²⁵ chloroaurates, and bromoaurates have been used occasionally, together with chlorides and bromides, if they are crystalline.

¹⁹⁵ H. Hellmann and G. Opitz, *Angew. Chem.* **68**, 265 (1956).

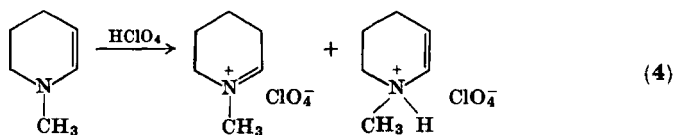
Indole and alkyl-indoles (**38**) are protonated in position 3 by the action of strong mineral acids.^{196, 197} The tendency of the enamine salts to assume the immonium structure is very general: the salts of ethyl β -aminocrotonate are derived from the imino form at the expense of the conjugation between the carbonyl group and the double bond.^{12, 198}



Addition takes place at the nitrogen atom, because of steric factors, in derivatives of dehydroquinuclidine and some polycyclic alkaloids such as trimethylconkurchine, neostrychnine, etc.³⁷ A curious formation of a nortricyclene derivative from 2-*N*-hexamethyleneimino-bicyclo[1,2,2]-2-heptene (**39**) on treatment with perchloric acid¹⁹⁹ has been claimed.



Though 1-methyl-2-alkyl- Δ^2 -piperideines react with acids to yield only the immonium salts, a mixture of the ammonium and immonium perchlorates is obtained from piperideines unsubstituted in position 2¹ (Eq. 4).



Immonium salts may be secondary protonation products, ammonium salt formation occurring first. Thus, immonium salts of

¹⁹⁶ R. L. Hinman and E. B. Whipple, *J. Am. Chem. Soc.* **84**, 2534 (1962).

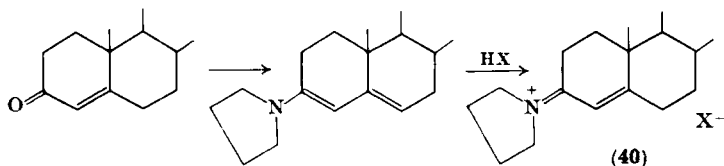
¹⁹⁷ R. L. Hinman and J. Lang, *Tetrahedron Letters* No. 21, 12 (1960).

¹⁹⁸ C. F. Hammer and R. A. Hines, *J. Amer. Chem. Soc.* **77**, 3649 (1955).

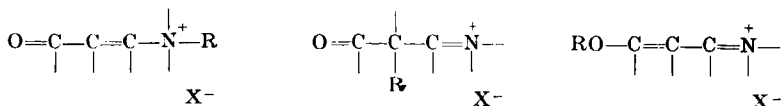
¹⁹⁹ A. G. Cook, *J. Am. Chem. Soc.* **85**, 648 (1963).

mineral acids from aliphatic dienamines (prepared from secondary amines and crotonaldehyde, 2-ethyl-2-hexenal, or isophorone) are not formed directly by the addition of a proton at C(4) of the dienamines, but by a rearrangement of the intermediate dienammonium salts.⁵⁹ In contrast, organic acids (acetic acid and benzoic acid) afford immonium salts⁶⁰ with isolated double bonds by a direct addition of the proton at C(2). In the reduction of dienamines with formic acid, the protons seem to add to both C(2) and C(4).

Dienamines derived from Δ^4 -3-oxosteroids give as the final products immonium salts with a system of conjugated double bonds (40), as shown by ultraviolet spectroscopy.³²



If other groups capable of conjugation are adjacent to the enamine system, they can also participate in the salt formation. Thus, in β -amino- α,β -unsaturated ketones, in addition to possible protonation at the α -carbon and the nitrogen, protonation could also occur on the carbonyl oxygen.²⁰⁰⁻²⁰²



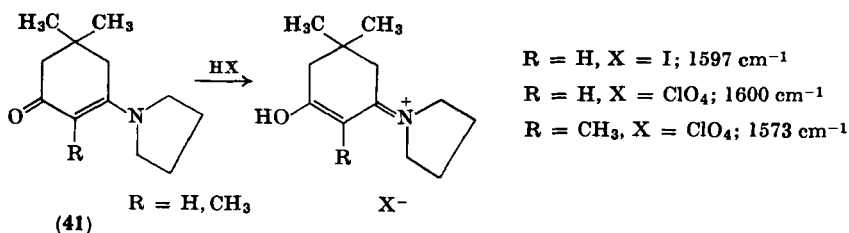
The infrared spectra of hydroiodides and perchlorates of such enamines indicate *O*-protonation; one or two strong maxima occur in the 1600 cm^{-1} region and there is no absorption in the $1650\text{--}1800\text{ cm}^{-1}$ region as would be expected for the ammonium or immonium compounds. 2,5,5-Trimethyl-3-pyrrolidino-2-cyclohexenone and 5,5-dimethyl-3-pyrrolidino-2-cyclohexenone (41) are examples of compounds which form salts by *O*-protonation. In contrast,

²⁰⁰ N. K. Kochetkov, M. G. Ivanova, and A. N. Nesmejanov, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk* 676 (1956).

²⁰¹ N. H. Cromwell, F. A. Miller, A. R. Johnson, R. L. Frank, and D. J. Wallace, *J. Am. Chem. Soc.* **71**, 3337 (1949).

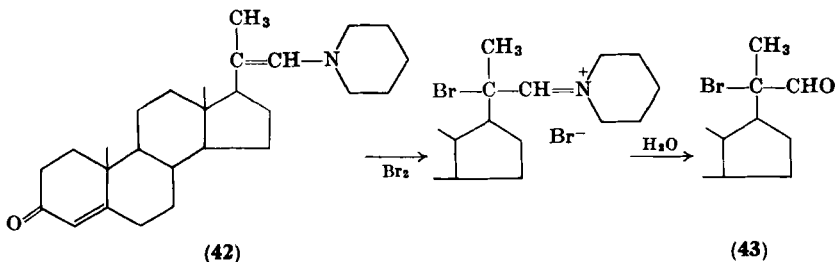
²⁰² N. J. Leonard and J. A. Adameik, *J. Am. Chem. Soc.* **81**, 595 (1959).

4-diethylamino-3-penten-2-one is obviously *C*- or *N*-protonated because bands occur at 1713 and 1672 cm^{-1} in the infrared spectrum of the salt.²⁰³



2. Addition of Halogens to the Double Bond of Enamines

The addition of bromine to 22-(1-piperidyl)bisnor-4,20(22)-choleadien-3-one (42) is formally analogous to salt formation. On hydrolysis of the intermediate β -bromo-immonium salt, 3-oxo-20-bromobisnor-4-chole-22-al (43) was obtained.²⁰⁴



3. Alkylation

One of the first recorded alkylations of the enamine system was the treatment of dihydroberberine or its alkylated derivatives with alkyl iodides: alkylation on the β -carbon atom prevailed.²⁰⁵ Later, many similar observations were published. Zatti and Ferratini²⁰⁶ showed that 1,3,3-trimethyl-2-methyleneindoline ("Fischer's base") and methyl iodide did not afford a quaternary salt but rather a tertiary base, 1,3,3-trimethyl-2-isopropylideneindoline, which is a product of

²⁰³ N. K. Kochetkov, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk* 47 (1954).

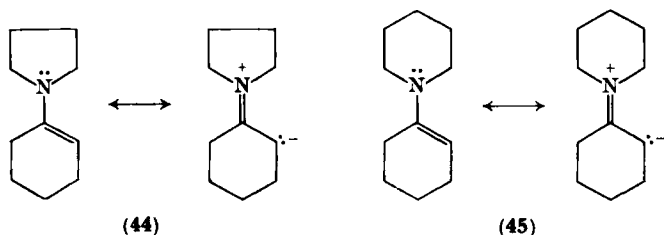
²⁰⁴ R. L. Pederson, J. L. Johnson, R. P. Holysz, and A. C. Ott, *J. Am. Chem. Soc.* 79, 1115 (1957).

²⁰⁵ J. Gadamer, *Arch. Pharm.* 248, 680 (1911).

²⁰⁶ C. Zatti and A. Ferratini, *Ber.* 23, 2302 (1890).

bis-alkylation on the carbon atom, as demonstrated by Plancher.²⁰⁷ *C*-Alkylation of β -aminocrotonic acid esters was studied by Robinson²⁰⁸ and, further, by Lauer and Lones.²⁰⁹ A systematic study of enamine alkylation began in 1954 when a method for the alkylation of ketones via enamines was worked out by Stork.⁷⁵ All enamines do not react in the same manner. Whether *N*- or *C*- β -alkylation occurs depends on the reactivity of the alkylating reagent, the structure of the alkylated enamine, and the polarity of the solvent.

Alkylation of enamines prepared from aldehydes was studied by Elkik,²¹⁰ Opitz and Mildenberg,²¹¹ and Williamson²¹² and alkylation of enamines prepared from ketones by Stork *et al.*⁷⁵ These investigators demonstrated that the ease of alkylation depends on the basicity of the enamine in question. Enamines prepared from the more basic pyrrolidine are alkylated more readily than those obtained from morpholine. Better yields of the enamines (44) from pyrrolidine are obtained, in contrast to the preparations (45) from piperidine (which are bases about as strong as pyrrolidine); this may result from the stabilizing influence of the exocyclic double bond in the polarized form of the pyrrolidine derivative.



C-Alkylation affords monoalkylated products as a result of the lower reactivity of the monoalkylated enamines. Enamine salts obtained by alkylation can afford new enamines capable of further alkylation only by the loss of a proton. In some cases, dialkylation can be achieved by the addition of the more basic ethyldicyclohexylamine. Monoalkylation of the pyrrolidine enamine of cyclohexanone is due to a considerable energy difference between the transition states caused

²⁰⁷ G. Plancher, *Ber.* **31**, 1488 (1898).

²⁰⁸ R. Robinson, *J. Chem. Soc.* **109**, 1038 (1916).

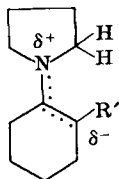
²⁰⁹ W. M. Lauer and G. W. Lones, *J. Am. Chem. Soc.* **59**, 232 (1937).

²¹⁰ E. Elkik, *Bull. Soc. Chim. France* p. 972 (1960).

²¹¹ G. Opitz and H. Mildenberg, *Angew. Chem.* **72**, 169 (1960).

²¹² W. R. N. Williamson, *Tetrahedron* **3**, 314 (1958).

by steric interactions of hydrogen atoms in the methylene groups vicinal to the pyrrolidine nitrogen atom with the substituents in the cyclohexane moiety. These interactions limit to a considerable extent the possibility of a planar polarized mesomeric form.²¹³



A practical application of the enamine alkylation is represented by the well-known Stork procedure of ketone alkylation. Its advantage, in comparison with the direct alkylation of carbonyl derivatives in the presence of strong bases, arises from the fact that monoalkylated derivatives are formed almost exclusively, avoiding the necessity for separation of polyalkylated products. According to Stork *et al.*,²¹³ the starting ketone is first treated with a cyclic secondary base (pyrrolidine, piperidine, or morpholine) to give an enamine, which is alkylated and the resulting immonium salt hydrolyzed with the formation of the desired α -alkylketone. In this manner, 70% of 2-methylcyclohexanone, 25% of 2-ethylcyclohexanone, and 36% of 2-propylcyclohexanone were obtained from 1-pyrrolidino-1-cyclohexene and methyl, ethyl, and *n*-propyl iodide in dioxane.^{214, 215} Any dialkylation occurs on the carbon atom which possesses the least substituents; this is in contrast to direct alkylation in the presence of a mineral base. Thus, 2-methylcyclohexanone affords 2,6-dimethylcyclohexanone (**46**) by the Stork procedure, whereas by the action of methyl iodide in a solution of alkali hydroxides, 2,2-dimethylcyclohexanone (**47**) is obtained.^{216, 217}

From a preparative point of view, the course of the alkylation can be undesirably influenced by the structural arrangement of the starting enamine. Thus, treatment of 1-pyrrolidino-1-cycloheptene with ethyl iodide, followed by hydrolysis, gives about 40% of 2-ethylcyclo-

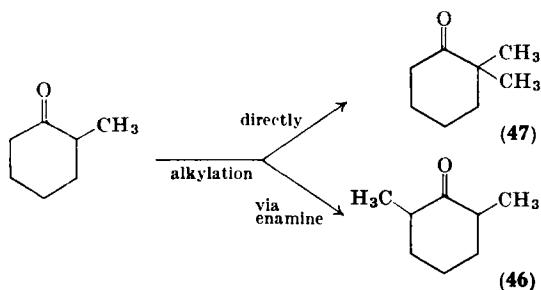
²¹³ G. Stork, R. Terrell, and J. Szmuszkowicz, *J. Am. Chem. Soc.* **76**, 2029 (1954).

²¹⁴ A. J. Speziale and R. C. Freeman, *J. Am. Chem. Soc.* **82**, 909 (1960).

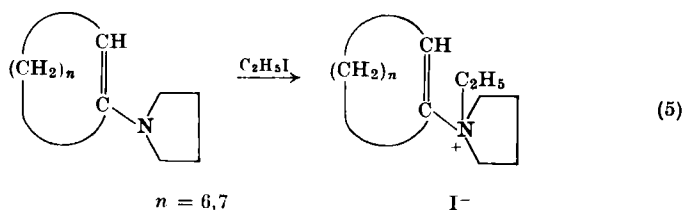
²¹⁵ G. Opitz, H. Mildenberg, and H. Suhr, *Ann. Chem.* **649**, 47 (1961).

²¹⁶ R. L. Frank and R. C. Pierle, *J. Am. Chem. Soc.* **73**, 724 (1951).

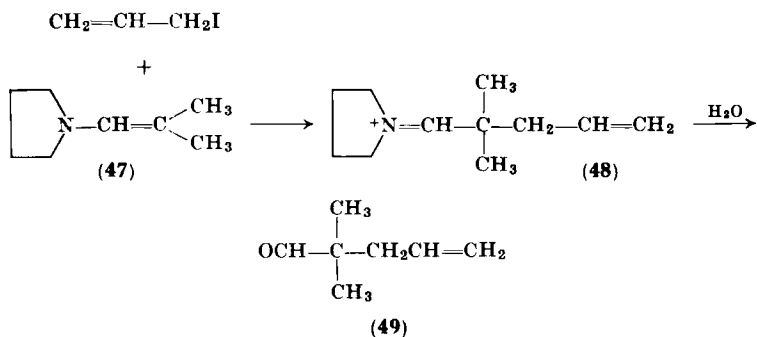
²¹⁷ J. M. Conia, *Bull. Soc. Chim. France* p. 533 (1950).



heptanone, whereas 1-pyrrolidino-1-cyclooctene and 1-pyrrolidino-1-cyclononene afford *N*-alkylated products only, and almost quantitatively, under analogous conditions²¹⁵ (Eq. 5). The cause lies in the peculiar conformation of medium-sized rings.



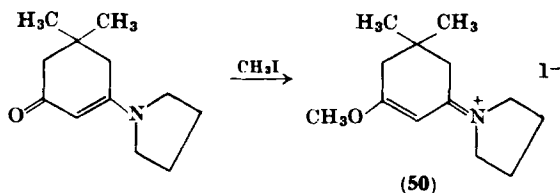
The enamines prepared from acetaldehyde or monosubstituted acetaldehydes undergo self-condensation in the reaction mixture very readily so that alkylation is practically impossible. Enamines prepared from disubstituted aldehydes are exclusively *N*-alkylated on treatment with aliphatic alkyl halides,²¹⁸ whereas allyl halides cause



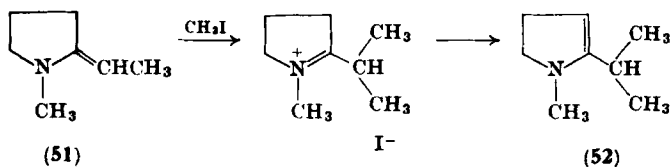
²¹⁸ G. Opitz and H. Mildenberg, *Ann. Chem.* **649**, 26 (1961).

²²² J. J. Panouse and J. Sannié, *Bull. Soc. Chim. France* p. 1374 (1956).

iodide, obtained only *C*-alkylation, in contrast to the experiments of Leonard and Adameik²⁰² with cyclic unsaturated enamines, e.g. 5,5-dimethyl-3-pyrrolidino-2-cyclohexenone, where *O*-alkylation products (**50**) were isolated. Determination of whether the enamine has been *O*-, *C*-, or *N*-alkylated follows from comparisons of the infrared spectra of the alkylation product and the analogous enamine salt according to the criteria mentioned in the discussion of protonation (Section II, B).



Alkylation of heterocyclic enamines proceeds similarly to the alkylation of "Fischer's base" discussed above. Lukeš and Dědek²²³ obtained on methylation of 1-methyl-2-ethylidenepyrrolidine (**51**) a *C*-alkylation product, i.e. 1-methyl-2-isopropyl- Δ^2 -pyrroline (**52**). Alkylation of the same enamine with ethyl bromoacetate²²⁴ was the first synthetic step in the preparation of DL-pseudoheliotridane.

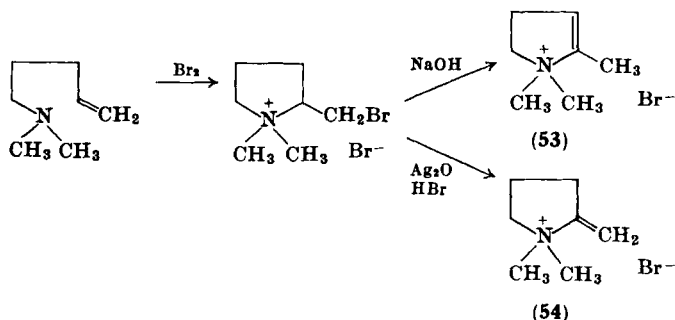


Quaternary ammonium salts of such bases could be prepared only indirectly; addition of bromine to 1-dimethylamino-4-pentene, followed by removal of hydrogen bromide, afforded—according to the dehydrohalogenation conditions—quaternary ammonium salts (**53** or **54**) derived from 1,2-dimethyl- Δ^2 -pyrroline or 1-methyl-2-methylenepyrrolidine.²²⁵

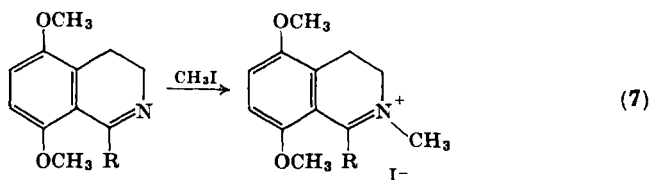
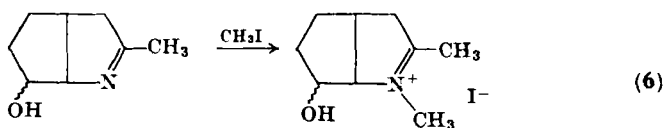
²²³ R. Lukeš and V. Dědek, *Chem. Listy* **51**, 2059 (1957); *Collection Czech. Chem. Commun.* **23**, 2046 (1958).

²²⁴ O. Červinka, *Chem. Listy* **52**, 307 (1958).

²²⁵ R. Lukeš and O. Červinka, *Chem. Listy* **47**, 392 (1953).



Most pyrrolines and piperideines which are not alkylated on the nitrogen atom occur exclusively in the imino form and afford quaternary immonium salts on alkylation²²⁶⁻²²⁸ (e.g., Eqs. 6 and 7).



When mesomerism is precluded sterically, enamines are alkylated solely on the nitrogen atom, cf. the methylation of neostrychnine with methyl iodide.²²⁹ Explanation of the exclusive *N*-methylation of $\Delta^{1(9)}$ -dehydroquinolizidine (36)¹⁷² and 1,2-dimethyl- Δ^2 -piperideine (68)²²⁹ is more difficult.

Of all the alkylating reagents used, saturated aliphatic halides are the most prone to react with the nitrogen atom and give a quaternary ammonium salt. Reactive halides of the allyl type, propargyl bromide,

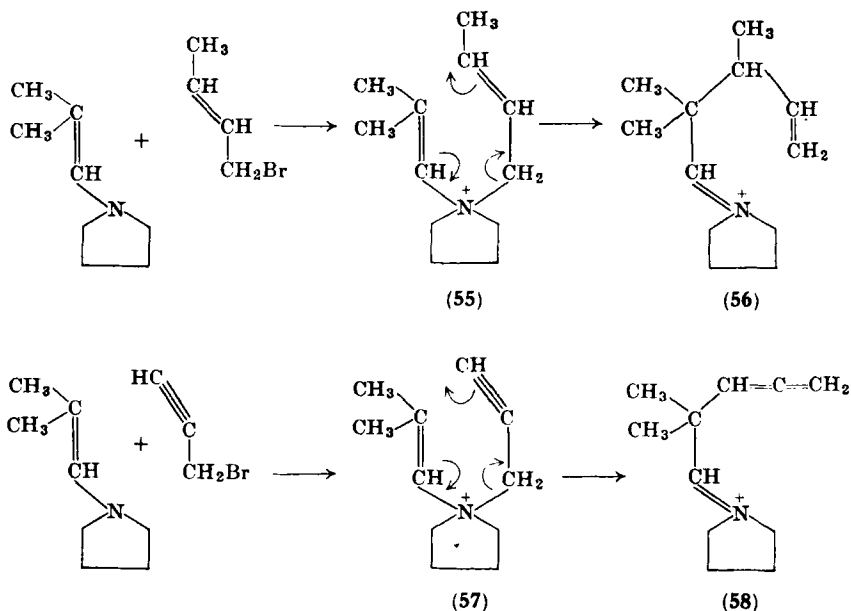
²²⁶ R. Griot and T. Wagner-Jauregg, *Helv. Chim. Acta* **42**, 605 (1959).

²²⁷ M. Lora-Tamayo, R. Madroñero, and M. Stud, *Chem. Ber.* **95**, 2176 (1962).

²²⁸ D. Béke and L. Töke, *Chem. Ber.* **95**, 2123 (1962).

²²⁹ O. Achmatowicz, G. R. Clemons, W. H. Perkin, Jr., and R. Robinson, *J. Chem. Soc.* **129**, 767 (1932).

α -halogeno-ethers, α -halogeno-ketones, α -halogeno-nitriles, and α -halogeno-esters, almost always react with the β -carbon atom of the enamine system. *C*-Alkylation of enamines derived from cyclic ketones and allylic halides or propargyl bromide proceeds without rearrangement. However, alkylation of enamines from disubstituted acetaldehydes is accompanied by an allylic or propargyl-allene rearrangement.^{230, 231} The reaction proceeds analogously to the Claisen rearrangement of phenolic allyl ethers. An α,β -unsaturated quaternary ammonium salt (55 or 57) is formed first and is then rearranged (cyclic mechanism) to the immonium salt (56 or 58).



Alkylations may be followed by subsequent reactions, e.g. cyclization. Thus, treatment of ω,ω' -dihalogenoalkanes with 1-pyrrolidino-1-cyclohexene, followed by hydrolysis, affords, in addition to other products, bicyclic ketones.²³² An interesting cyclization was described by Parcell²³³ in connection with the alkylation of 1-piperidino-1-

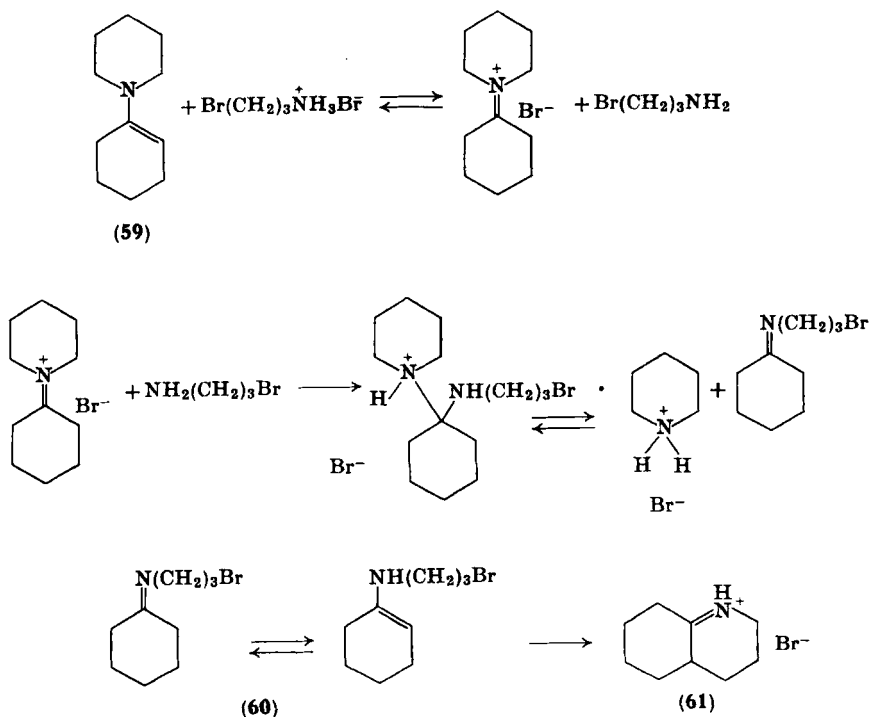
²³⁰ G. Opitz, *Ann. Chem.* **650**, 122 (1961).

²³¹ K. C. Brannock and R. D. Burpitt, *J. Org. Chem.* **26**, 3576 (1961).

²³² G. Opitz and H. Mildenberg, *Ann. Chem.* **650**, 115 (1961).

²³³ R. F. Parcell, *J. Am. Chem. Soc.* **81**, 2596 (1959).

cyclohexene (59) by 3-diethylaminopropyl bromide. The expected 2-(3-diethylaminopropyl)cyclohexanone is obtained; but with the 3-aminopropyl bromide hydrobromide, $\Delta^{1(9)}$ -octahydroquinone (61) is formed. A proton is first eliminated from the 3-bromopropylammonium ion by the more basic enamine. The free 3-bromopropylamine then reacts with the resulting enamine salt to eliminate piperidine hydrobromide, and the intermediate *N*-cyclohexylidene-3-bromopropylamine (60) is finally cyclized in the enamine form.



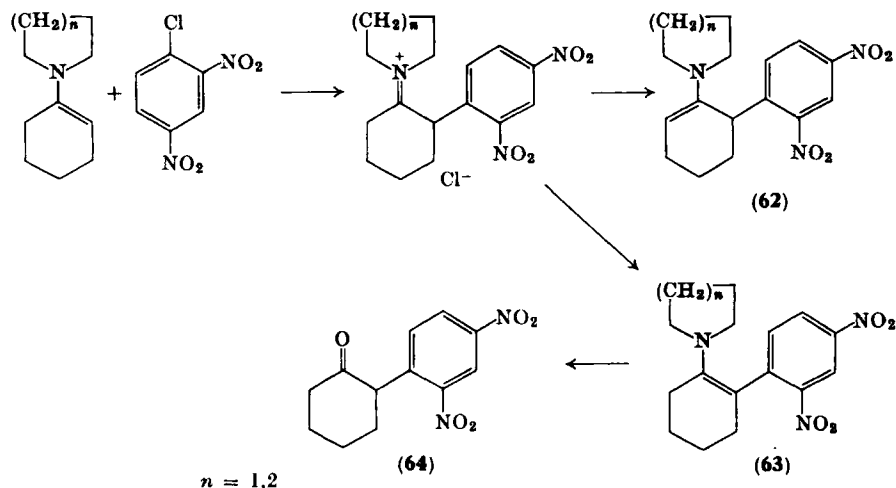
4. Arylation

Arylation of enamines²³⁴ represents an analogy of the Stork reaction.²³⁵ Reactive aryl halides usually cause *C*-arylation. Treatment of 2,4-dinitrochlorobenzene with 1-pyrrolidino-1-cyclohexene affords 2-(2,4-dinitrophenyl)cyclohexanone (64) in very good yield. As

²³⁴ M. E. Kuehne, *J. Am. Chem. Soc.* **84**, 837 (1962).

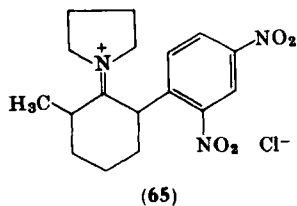
²³⁵ A. R. Surrey, "Name Reactions in Organic Chemistry." Academic Press, New York, 1961.

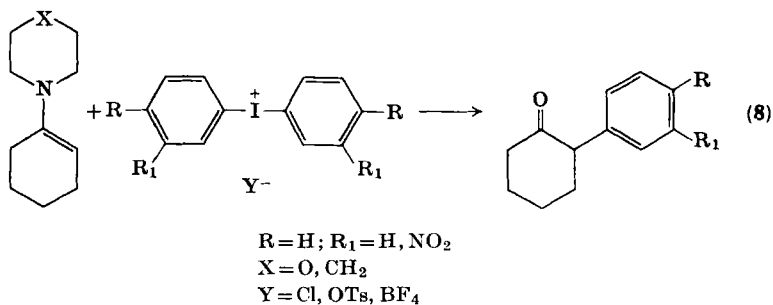
expected, the reaction proceeds well in dichloromethane or dioxane, and less readily in benzene. If piperidine is used for the preparation of the starting enamine, the yields are lower; with morpholine as a component, the reaction does not take place at all.



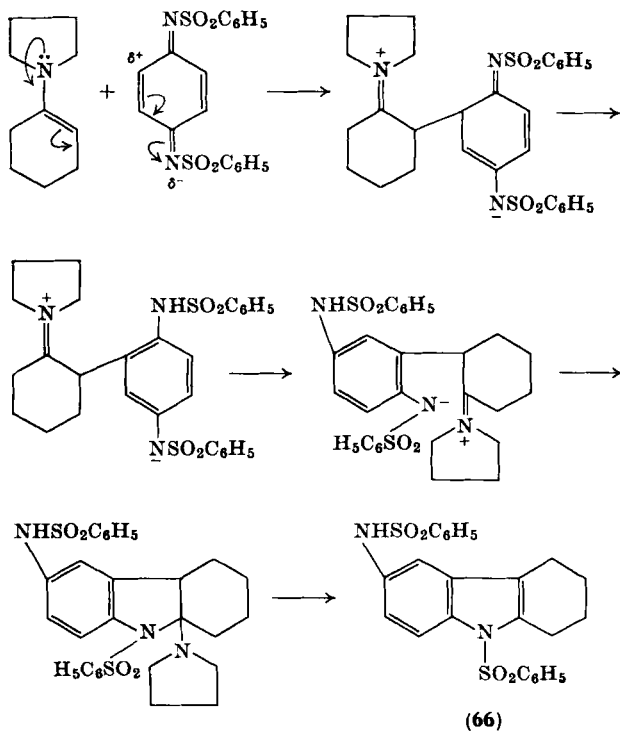
The monoarylated enamine can then be acylated to form a mixture of 2-acyl-2-arylcyclohexanone and 2-aryl-6-acylcyclohexanone. This was held to indicate that arylation affords two enamines, **62** and **63**, which differ only in the position of the double bond. The reaction involving acyl halides could be explained under the assumption that in the more probable enamine structure (with conjugation through the free electron pair on nitrogen, the double bond, and the aromatic ring) it is the hydrogen atom on C(6) which is more acidic.

The enamine obtained from pyrrolidine and 2-methylcyclohexanone is arylated, as expected, in the 6-position (**65**).





C-Arylation also takes place with other reactive halides, e.g. heterocyclic 2-chloro-5-nitropyridine 4-chloro-3-nitropyridine, and 2-chloro-4,5-dicarbethoxypyrimidine. 2,4-Dinitrofluorobenzene leads to resinous products, because it is too reactive. Arylation of enamines with less reactive halides occur solely at nitrogen. Treatment of 1-pyrrolidino-1-cyclohexene with 4-nitrochlorobenzene at elevated temperatures affords *N*-4-nitrophenylpyrrolidine. The first step probably consists



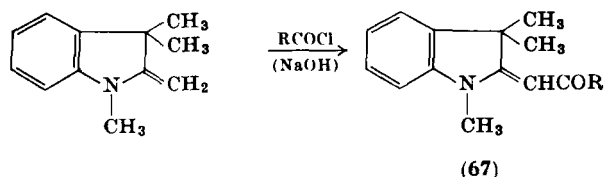
of *N*-arylation with the formation of an enamine salt, which is then cleaved by hydrogen migration.

Arylation of enamines can also be achieved with iodonium salts²³⁴ (Eq. 8) but the yields are low.

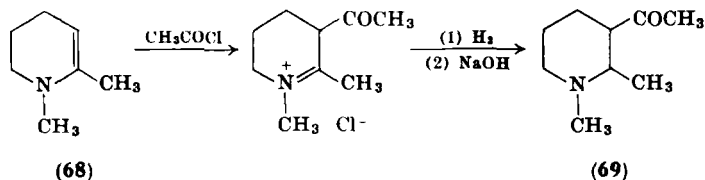
The complicated reaction of 1-pyrrolidino-1-cyclohexene with quinonebenzenesulfonimide may begin with arylation of the enamine system.²³⁴ The final product of the strongly exothermic reaction is a substituted tetrahydrocarbazole (66).

5. Acylation

Acylation of enamines is to a great extent similar to alkylation, and usually occurs on the β -carbon atom of the enamine. There are few reports about the acylation of enamines of the pyrroline and piperidine type. Acylation of 1,3,3-trimethyl-2-methyleneindoline leads to 1,3,3-trimethyl-2-acylmethyleneindoline (67).²³⁶ 1,2-Dimethyl-3-



acetylpiperidine (69) has been prepared by acetylation of 1,2-dimethyl- Δ^2 -piperidine (68), followed by hydrogenation.³⁸



In contrast, acid chlorides normally add to Schiff bases.^{237, 238} Ring-opening occurs on treatment of 2-alkyl- Δ^1 -pyrrolines and 2-alkyl- Δ^1 -piperideines with acid chlorides.²³⁹⁻²⁴¹

²³⁶ M. Coenen, *Angew. Chem.* **61**, 11 (1949).

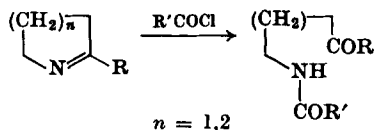
²³⁷ H. Breederveld, *Rec. Trav. Chim.* **79**, 1197 (1960).

²³⁸ H. Böhme and K. Hartke, *Chem. Ber.* **96**, 600 (1963).

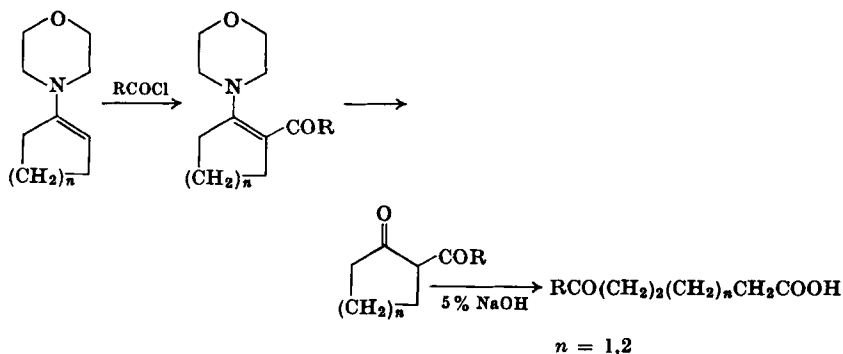
²³⁹ M. C. Kloetzel and J. L. Pinkus, *J. Am. Chem. Soc.* **80**, 2332 (1958).

²⁴⁰ S. Gabriel and J. Colman, *Ber.* **41**, 513 (1908).

²⁴¹ A. Lipp, *Ann. Chem.* **289**, 173 (1896).



From a preparative point of view, the acylation of ketones via enamines is of particular interest. In comparison with pyrrolidine and piperidine enamines, the less reactive morpholine enamines give better yields, as found by Hünig *et al.*²⁴² β -Diketones are the products of acylation with an acyl halide followed by acid hydrolysis, whereas with ethyl chloroformate, β -ketoesters are obtained.²¹² Hünig and his collaborators²⁴²⁻²⁴⁷ have used the acylation of 1-morpholino-1-cyclopentene and 1-morpholino-1-cyclohexene to lengthen the chains of acids by five and six carbon atoms, respectively. The reaction may



also be used with dichlorides of dicarboxylic acids. (+)-Tuberculo-stearic acid has thus been prepared.²⁴⁸

The *C*-acyl derivatives constitute the regular products. Thus, acylation of 5,5-dimethyl-3-(1-pyrrolidyl)-2-cyclohexen-1-one with acetyl chloride or with chlorides of aromatic acids affords 2-acyl derivatives.^{248a} On the other hand, an analogous reaction with

²⁴² S. Hünig, E. Benzing, and E. Lücke, *Chem. Ber.* **90**, 2833 (1957).

²⁴³ S. Hünig, E. Lücke, and E. Benzing, *Chem. Ber.* **91**, 129 (1958).

²⁴⁴ S. Hünig and E. Lücke, *Chem. Ber.* **92**, 652 (1959).

²⁴⁵ S. Hünig and W. Lendle, *Chem. Ber.* **93**, 909 (1960).

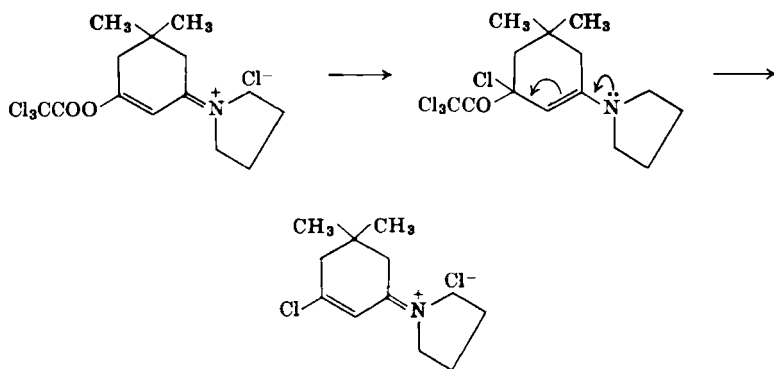
²⁴⁶ S. Hünig and W. Lendle, *Chem. Ber.* **93**, 913 (1960).

²⁴⁷ S. Hünig and W. Eckardt, *Chem. Ber.* **95**, 2493 (1962).

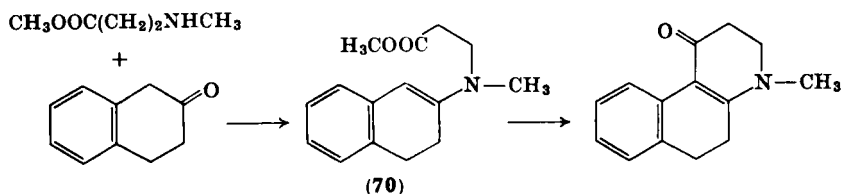
²⁴⁸ S. Hünig and M. Salzwedel, *Angew. Chem.* **71**, 339 (1959).

^{248a} G. H. Alt and A. J. Speziale, *Tetrahedron Letters* No. 2, 111 (1963).

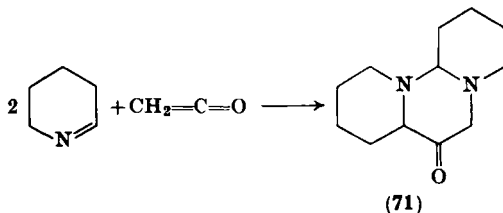
trichloroacetyl chloride leads to 1-(3-chloro-5,5-dimethyl-2-cyclohexen-1-ylidene)pyrrolidinium chloride.^{248b}



Sometimes acid anhydrides may be used as acylating reagents. The mixed anhydride of formic and acetic acid reacts with the enamines prepared from cyclohexanone to give 50% of hydroxymethylene-cyclohexanone.²¹² An intramolecular acylation with an ester (70) has also been reported.²⁴⁹



Ketene reacts²⁵⁰ with two molecules of Δ^1 -piperidine to form a tricyclic derivative (71).



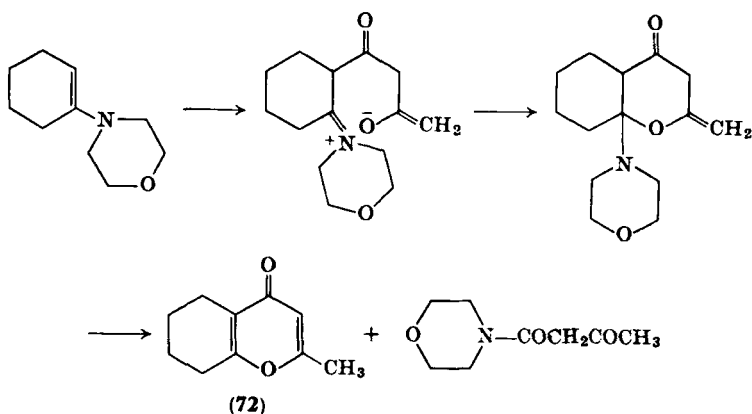
^{248b} G. H. Alt and A. J. Speziale, *J. Org. Chem.* **29**, 794, 798 (1964).

²⁴⁹ N. A. Nelson, J. E. Ladbury, and R. S. P. Hsi, *J. Am. Chem. Soc.* **80**, 6633 (1958).

²⁵⁰ J. Thesing and K. Hofmann, *Chem. Ber.* **90**, 229 (1957).

Treatment of 1-morpholino-1-cyclohexene with ketene gives 1-morpholino-2-acetyl-1-cyclohexene²⁵¹ as the main product, whereas enamines prepared from aliphatic aldehydes yield cyclobutanones.^{252, 253} Ketene may be generated directly in the reaction medium from acid chlorides and triethylamine.

1,3,3-Trimethyl-2-methyleneindoline reacts with diketene as expected. 1-Morpholino-1-cyclohexene and 1-morpholino-1-cyclopentene afford 2-methyl-5,6,7,8-tetrahydrochromone (72) and 2-methyl-5,6-trimethylene-4-pyrone, respectively, on treatment with diketene.



The enolate of the acylated intermediate is cyclized with elimination of morpholine and double bond isomerization.²⁵³⁻²⁵⁵ A similar formation of a dihydrochromone from 2,3-dimethyldihydroaniline has been reported by Millward.²⁵⁶

Treatment of 1-morpholinocyclohexene with chlorocyanogen, followed by hydrolysis, gave the expected 2-cyanocyclohexanone (Kuehne⁷⁸). The reported (Fusco *et al.*²⁵⁷) formation of 2-chlorocyclohexanone appears unlikely.

²⁵¹ B. Eistert and R. Wessendorf, *Chem. Ber.* **94**, 2590 (1961).

²⁵² G. Opitz, M. Kleemann, and F. Zimmermann, *Angew. Chem.* **73**, 654 (1961).

²⁵³ G. Opitz and F. Zimmermann, *Ann. Chem.* **662**, 178 (1963).

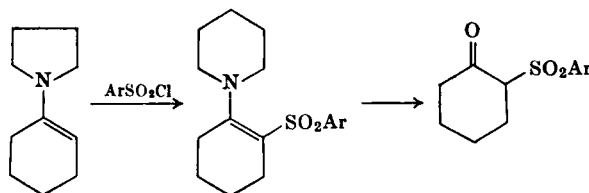
²⁵⁴ S. Hünig, *Angew. Chem.* **71**, 312 (1959).

²⁵⁵ S. Hünig, E. Benzing, and K. Hübner, *Chem. Ber.* **94**, 486 (1961).

²⁵⁶ B. B. Millward, *J. Chem. Soc.* p. 26 (1960).

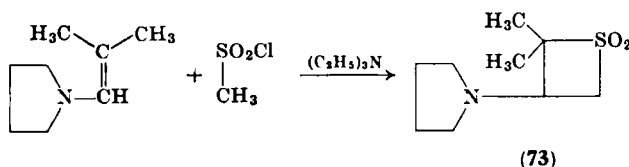
²⁵⁷ R. Fusco, S. Rossi, and G. Bianchetti, *Gazz. Chim. Ital.* **91**, 841 (1961).

Treatment of enamines with sulfonyl chlorides, followed by hydrolysis, leads to β -ketosulfones²⁵⁸ (Scheme 8).



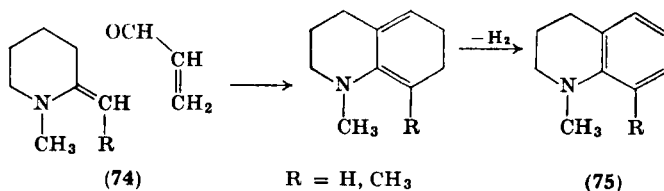
SCHEME 8

Treatment of methanesulfonyl chloride with 1-morpholinocyclohexene²⁵⁸ or 1-pyrrolidinoisobutene²⁵⁹ at 25° in the presence of triethylamine affords aminosulfones with a four-membered ring (**73**). The intermediate formation of the sulfene $\text{CH}_2=\text{SO}_2$ is possible in this reaction.



6. Reactions with α,β -Unsaturated Compounds

Because of the conjugation of the free electron pair on the nitrogen atom with the double bond, enamines react very readily with double bonds activated by electronegative groups. Addition of acrolein to 1-methyl-2-ethylidenepyrrolidine, followed by dehydrogenation, led to 1,7-dimethylindole.²⁶⁰ In a similar addition to 1-methyl-2-alkyl- Δ^2 -piperidineines, 1-methyl-8-alkyl-1,2,3,4-tetrahydroquinolines (**75**) were obtained.³⁸ In the reaction scheme, the starting bases are considered to react as the tautomeric 1-methyl-2-alkylidenepiperidines (**74**).

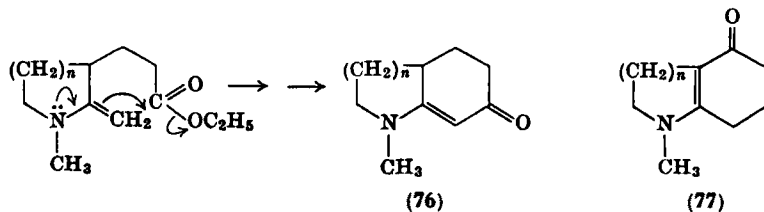


²⁵⁸ G. Stork and I. J. Borowitz, *J. Am. Chem. Soc.* **84**, 313 (1962).

²⁵⁹ G. Opitz and H. Adolph, *Angew. Chem.* **74**, 77 (1962).

²⁶⁰ R. E. Ireland, *Chem. & Ind. (London)* p. 979 (1958).

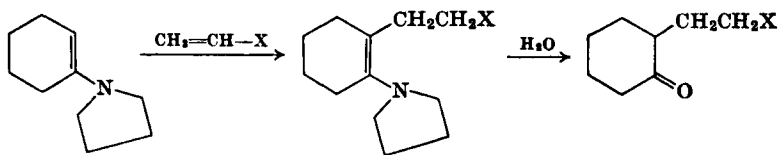
The addition of ethyl acrylate to 1,2-dimethyl- Δ^2 -piperidine,³⁸ 1-methyl-2-ethyl- Δ^2 -piperidine,³⁹ and 1,2-dimethyl- Δ^2 -pyrroline^{261, 262} occurs with both possible enamine structures in each case. Addition to 1,2-dimethyl- Δ^2 -piperidine or 1,2-dimethyl- Δ^2 -pyrroline is followed by intramolecular acylation by the ester group as a side-reaction to give **76** or **77**, respectively.



An interesting addition of ethyl acrylate has been reported in the case of 1-methyl-2-ethylidenepyrrolidine. An unsaturated amino-ketone is formed, which rearranges to 1,7-dimethyltetrahydroindole on reduction with formic acid, as established by dehydrogenation to 1,7-dimethylindole.²⁶²

An acid-catalyzed addition of methyl vinyl ketone to indole and 2-methylindole has been reported by Szmuszkowicz.²⁶³

Stork has used the addition of α,β -unsaturated aldehydes, ketones, esters, and nitriles to enamines prepared from ketones and pyrrolidine, piperidine, or morpholine for the synthesis of α -substituted carbonyl compounds^{264, 265} (Scheme 9).



SCHEME 9. X = CHO, COR, COOR, CN.

Polar solvents facilitate these additions. The addition of acrylonitrile or ethyl acrylate to 1-pyrrolidinocyclohexene shows marked solvent dependence. In dioxane as solvent, an 80% yield of monocyano- or

²⁶¹ O. Červinka, *Chem. & Ind. (London)* p. 1129 (1959).

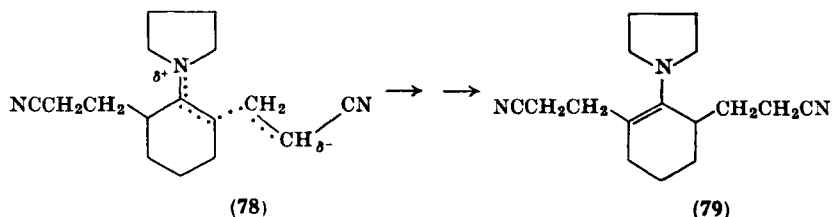
²⁶² O. Červinka, *Collection Czech. Chem. Commun.* **25**, 1183 (1960).

²⁶³ J. Szmuszkowicz, *J. Am. Chem. Soc.* **79**, 2819 (1957).

²⁶⁴ G. Stork and H. K. Landesman, *J. Am. Chem. Soc.* **78**, 5129 (1956).

²⁶⁵ L. A. Cohen and B. Witkop, *J. Am. Chem. Soc.* **77**, 6595 (1955).

carboethoxy-alkylated products was obtained, but the 2,6-dialkylated compound (79) was the main product in ethanol. The more polar ethanol apparently facilitates proton loss and hence the formation of the dialkylated product via 78.^{75, 212}



The intermediate alkylation products from enamines are hydrolyzed, even by water.²⁶⁶ The adducts with α,β -unsaturated ketones are more stable, and in this case hydrolysis by aqueous acetic acid—sodium acetate is required.³² Further condensation to give bicyclic unsaturated ketones frequently occurs.^{267, 268}

Enamines of aldehydes react with alkyl vinyl ketones.²¹² Substituted cyclohexanones may be obtained after hydrolysis. Application of this reaction to α,β -unsaturated aldehydes leads to substituted glutardialdehydes.²⁶⁹ The ratio of the products from the addition of methyl vinyl ketone to the pyrrolidine enamine derived from β -decalone depends on the configuration of the decalone.⁷⁵

In some additions of acrylonitrile, cyclobutanes²⁷⁰ are formed by addition of the intermediate anion to the —C=N— group. This formation was established by means of nuclear magnetic resonance spectra and, in some cases, by isolation.^{270a-d}

Addition of acrolein to 1-pyrrolidinocyclohexene leads to a tricyclic

²⁶⁶ A. J. Birch, P. Hextall, and J. A. K. Quartey, *Australian J. Chem.* **6**, 445 (1953).

²⁶⁷ G. Stork and H. K. Landesman, *J. Am. Chem. Soc.* **78**, 5129 (1956).

²⁶⁸ V. Prelog and M. Zimmermann, *Helv. Chim. Acta* **32**, 2360 (1949).

²⁶⁹ G. Opitz and J. Löschmann, *Angew. Chem.* **72**, 523 (1960).

²⁷⁰ K. C. Brannock, A. Bell, R. D. Burpitt, and C. A. Kelly, *J. Org. Chem.* **26**, 625 (1961).

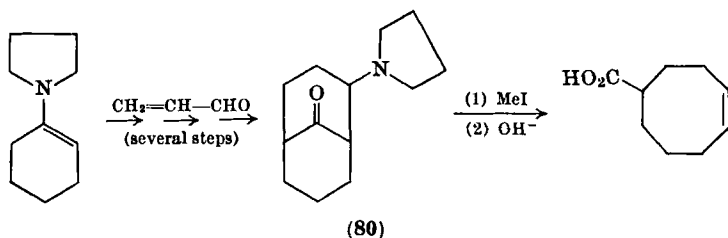
^{270a} I. Fleming and J. Harley-Mason, *J. Chem. Soc.* p. 2165 (1964).

^{270b} A. K. Bose, G. Mina, M. S. Manhas, and E. Rzuclido, *Tetrahedron Letters* No. **22**, 1467 (1963).

^{270c} G. A. Berchtold and G. F. Uhlig, *J. Org. Chem.* **28**, 1459 (1963).

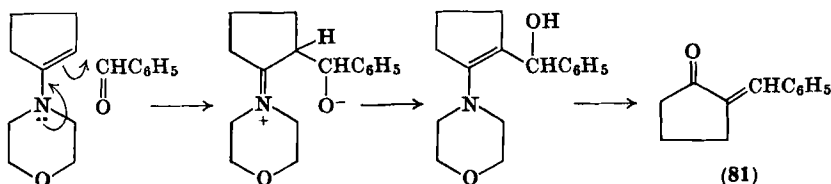
^{270d} L. C. Brannock, R. D. Burpitt, and J. G. Ohweatt, *J. Org. Chem.* **28**, 1462, 1463 (1963).

aminoketone (**80**) which, in turn, affords cyclooctene 5-carboxylic acid by the action of base on its *N*-methiodide (Stork and Landesman²⁶⁴). α,β -Unsaturated ketones add to the nitrogen atom of imines.²⁷¹

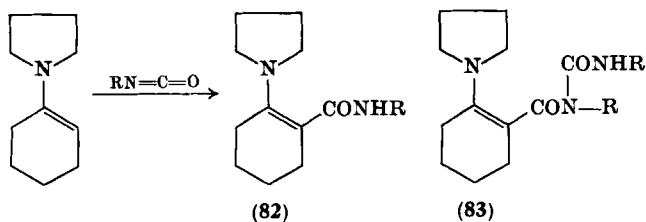


7. Reactions of Enamines with Other Electrophilic Reagents

Addition of aldehydes to enamines, followed by hydrolysis, leads to monoalkylidene and monoarylidene ketones (**81**).²⁷² An example in which this reaction occurs intramolecularly is provided by the alkaloid ajmaline.²⁷³



Addition of isocyanates and isothiocyanates, followed by hydrolysis, yields amides, thioamides,²⁷⁴⁻²⁷⁷ or ureides of β -ketoacids; **82** and **83** are examples of typical intermediates in this reaction.



²⁷¹ D. Béke and C. Szantay, *Chem. Ber.* **95**, 2132 (1962).

²⁷² L. Birkofer, S. M. Kim, and H. D. Engels, *Chem. Ber.* **95**, 1495 (1962).

²⁷³ M. F. Bartlett, B. F. Lambert, H. M. Weblood, and W. I. Taylor, *J. Am. Chem. Soc.* **85**, 475 (1963).

²⁷⁴ G. A. Berchtold, *J. Org. Chem.* **26**, 3043 (1961).

²⁷⁵ S. Hünig and K. Hübner, *Chem. Ber.* **95**, 937 (1962).

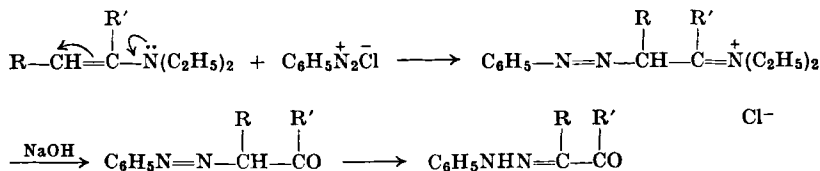
²⁷⁶ S. Hünig, K. Hübner, and E. Benzing, *Chem. Ber.* **95**, 926 (1962).

²⁷⁷ J. Goerdeler and H. W. Pohland, *Chem. Ber.* **96**, 526 (1963).

Addition of phenyl isocyanate to dimethylisobutenylamine yielded 1-phenyl-3,3-dimethyl-4-dimethylamino-2-azetidinone.²⁷⁸ The primary products of the addition of isocyanates to enamines may be converted into pyrimidine or pyrazole derivatives.²⁷⁹

Derivatives of triazole have been obtained by Fusco *et al.*²⁸⁰ from phenyl azide and 1-morpholinocyclohexene. Their decomposition leads to cyclopentanecarboxylic acid by elimination of nitrogen and ring contraction.²⁸¹ The dienamine obtained from piperidine and 2-ethyl-2-hexenal affords three isomeric triazolines on treatment with hydrazoic acid.²⁸²

Reactions of enamines with diazonium salts have also been reported. Treatment of benzenediazonium chloride with 1,3,3-trimethyl-2-methyleneindoline gave an azo compound,²⁸³ whereas with aliphatic enamines the final products were hydrazines of α -ketoaldehydes²⁸⁴ or α -diketones (Scheme 10).



SCHEME 10. R, R' = alkyl; R = alkyl, R' = H.

The curious reaction of benzyne with 1-pyrrolidinocyclohexene leads to a benzocyclobutane derivative in addition to a small amount of 2-phenyleyclohexanone.²³⁴

Oxygen may be added by means of peracids to the double bond of enamines prepared from 20-oxosteroids. The 17,20-epoxides obtained may be readily hydrolyzed to 17 α -hydroxy-20-oxosteroids.⁸⁶ Schiff bases afford oxaziranes on treatment with peracids.²⁸⁵ By means

²⁷⁸ M. Perelman and S. A. Mizesak, *J. Am. Chem. Soc.* **84**, 4989 (1962).

²⁷⁹ R. Fusco, G. Bianchetti, and S. Rossi, *Gazz. Chim. Ital.* **91**, 825 (1961).

²⁸⁰ R. Fusco, G. Bianchetti, and D. Pocar, *Gazz. Chim. Ital.* **91**, 1233 (1961); **91**, 849 (1961).

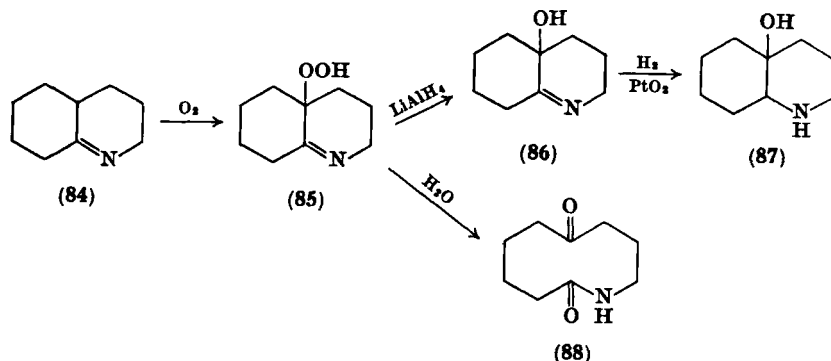
²⁸¹ R. Fusco, G. Bianchetti, and D. Pocar, *Gazz. Chim. Ital.* **91**, 933 (1961).

²⁸² G. Opitz and W. Merz, *Ann. Chem.* **652**, 158 (1962).

²⁸³ W. König and J. Müller, *Ber.* **57**, 144 (1924); W. König, *Ber.* **57**, 891 (1924).

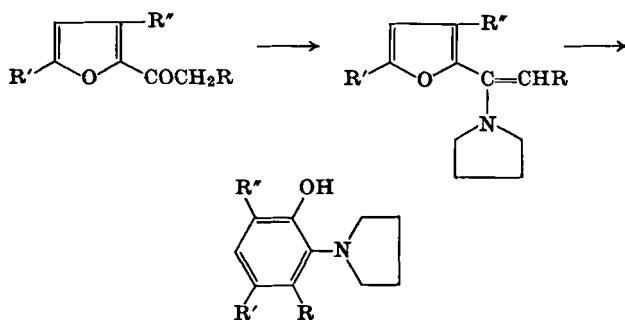
²⁸⁴ J. W. Cray, O. R. Quayle, and C. T. Lester, *J. Am. Chem. Soc.* **78**, 5584 (1956).

²⁸⁵ W. D. Emmons, *J. Am. Chem. Soc.* **79**, 5739 (1957).



of atmospheric oxygen, hydroperoxides are formed from the imines.^{13, 286-290} Thus, $\Delta^{1(9)}$ -octahydroquinoline (84) affords a crystalline hydroperoxide (85), which may be reduced to 10-hydroxy- $\Delta^{1(9)}$ -octahydroquinoline (86) or, finally, to 10-hydroxydecahydroquinoline (87). Hydrolysis of the hydroperoxide gave a cyclic oxolactam (88).

Formation of such lactams is a general reaction.²⁹¹⁻²⁹⁴ The hydroperoxide of 2,3-diethylindole also undergoes rearrangement and



SCHEME 11. $R = H, CH_3, C_6H_5$; $R' = R'' = H, \text{alkyl}$.

²⁸⁶ B. Witkop, *Ann. Chem.* **558**, 98 (1947).

²⁸⁷ B. Witkop, *Bull. Soc. Chim. France* p. 423 (1954).

²⁸⁸ B. Witkop, *J. Am. Chem. Soc.* **76**, 5597 (1954).

²⁸⁹ B. Witkop, *J. Am. Chem. Soc.* **72**, 2311 (1950).

²⁹⁰ C. L. Stevens and R. J. Gasser, *J. Am. Chem. Soc.* **79**, 6057 (1957).

²⁹¹ B. Witkop and J. B. Patrick, *J. Am. Chem. Soc.* **73**, 2188 (1951).

²⁹² B. Witkop and J. B. Patrick, *J. Am. Chem. Soc.* **73**, 2196 (1951).

²⁹³ B. Witkop, J. B. Patrick, and M. Rosenblum, *J. Am. Chem. Soc.* **73**, 2641 (1951).

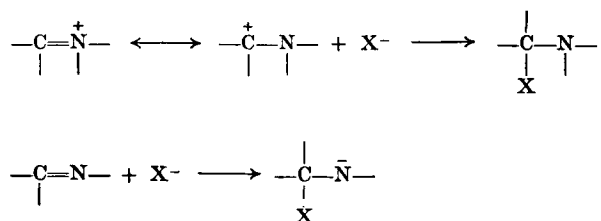
²⁹⁴ B. Witkop, *J. Am. Chem. Soc.* **72**, 1428 (1950).

cyclization.²⁹⁵ Reaction of enamines with dibenzoylperoxide gives 2-hydroxyketones.²⁹⁶

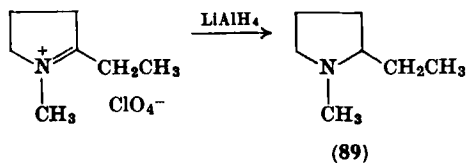
Enamines obtained from secondary amines and 2-acylfurans undergo the "acylfuran-enamine" rearrangement with the formation of *N*-substituted *o*-aminophenols²⁹⁷ (Scheme 11).

B. REACTIONS OF ENAMINE SALTS WITH NUCLEOPHILIC REAGENTS

Reactions at the carbon-nitrogen double bond are analogous to nucleophilic reactions at the carbonyl group of aldehydes and ketones. Free enamines normally do not react with nucleophilic reagents. Similar reactions occur as expected with the imino form of the *N*-substituted bases, although the reactivity of enamine salts towards nucleophiles is higher due to the positive charge on the nitrogen atom.



In contrast to the free bases, the salts of enamines are reduced by lithium aluminum hydride or sodium borohydride to saturated amines,^{298, 299} e.g. **89**.



Reduction of 1-methyl-2-alkyl- Δ^2 -piperidine perchlorates with complex hydrides prepared *in situ* by partial decomposition of

²⁹⁵ W. I. Taylor, *Proc. Chem. Soc.* p. 247 (1962).

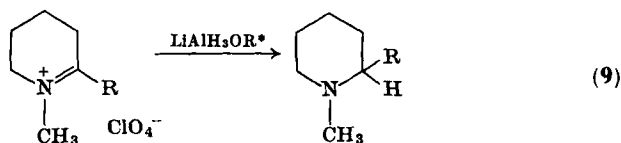
²⁹⁶ R. L. Augustine, *J. Org. Chem.* **28**, 581 (1963).

²⁹⁷ L. Birkofer and G. Daum, *Chem. Ber.* **95**, 183 (1962).

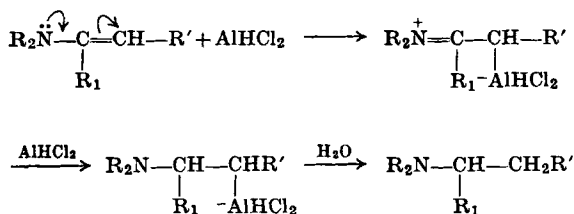
²⁹⁸ N. G. Gaylord, "Reduction with Complex Metal Hydrides," p. 781. Interscience, New York, 1956.

²⁹⁹ J. A. Marshall and W. S. Johnson, *J. Org. Chem.* **28**, 421 (1963).

lithium aluminum hydride with the optically active secondary alcohols (–)-menthol and (+)-borneol affords partially optically active 1-methyl-2-alkylpiperidine³⁰⁰ (Eq. 9). The procedure has been used for the synthesis of optically active bases and for the determination of their probable absolute configuration.



Surprising results have been encountered in the hydrogenolysis of enamines to alkenes in the course of their reduction with an 1:1 mixture of lithium aluminum hydride and aluminum chloride in ether.³⁰¹ From 1-pyrrolidinocyclopentene, 83% of cyclopentene was thus obtained. Formation of α -pyrrolidinocyclopentylaluminum chloride on addition of monochloroaluminum hydride to the enamine must be postulated, followed by decomposition of the intermediate complex to the cycloalkene. The single known instance of reduction of a free enamine is represented by the reaction with dichloroaluminum hydride.³⁰² Addition of the reagent leads to a complex which, on decomposition with water, affords the saturated base (Scheme 12).



SCHEME 12

The pyrrolines are also reduced with tin and hydrochloric acid,⁵ electrolytically,^{303, 304} or under Clemmensen conditions. The inter-

³⁰⁰ O. Červinka, *Collection Czech. Chem. Commun.* **26**, 673 (1961).

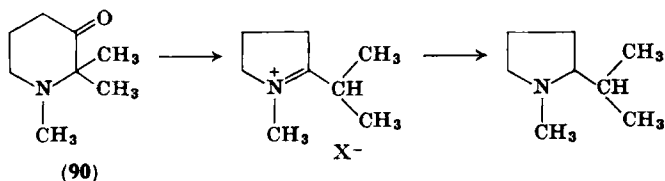
³⁰¹ J. W. Lewis and P. P. Lynch, *Proc. Chem. Soc.* p. 19 (1963).

³⁰² J. Samsonlet and Z. Welvart, *Bull. Soc. Chim. France* p. 77, (1962).

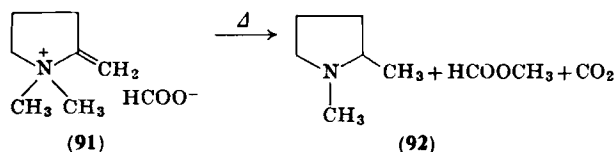
³⁰³ J. Tafel and M. Stern, *Ber.* **33**, 2224 (1900).

³⁰⁴ R. Lukeš, *Collection Czech. Chem. Commun.* **4**, 351 (1932); *Chem. Listy* **27**, 1 (1933).

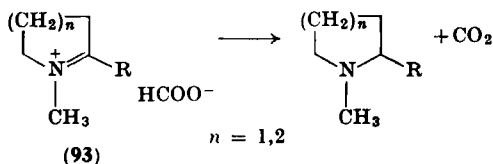
mediate formation of enamine salts is postulated in the reduction of α -amino-ketones (e.g. **90**) according to Clemmensen, proceeding with ring enlargement or contraction.^{305, 306} The apparently normal reduction of 3-oxoquinuclidine to quinuclidine³⁰⁷ is in fact exceptional and is probably due to steric effects.



Enamines are also reduced with formic acid, e.g. under the conditions of the Wallach-Leuckart reaction. The first reduction reported was the observation of Lukeš³⁰⁸ that the cleavage of 1,1-dimethyl-2-methylenepyrrolidinium formate (**91**) by dry distillation is accompanied by reduction with the formation of 1,2-dimethylpyrrolidine



(**92**) as the final product. A detailed study of the reduction of quaternary pyridinium salts with formic acid was consequently undertaken. Formic acid was used for the reduction of enamines by De Beneville and Macartney³⁰⁹ and, subsequently, by Leonard *et al.*³¹⁰ for com-



³⁰⁵ N. J. Leonard and E. Barthel, *J. Am. Chem. Soc.* **72**, 3632 (1950).

³⁰⁶ N. J. Leonard, J. W. Curry, and J. J. Sagura, *J. Am. Chem. Soc.* **75**, 6249 (1953).

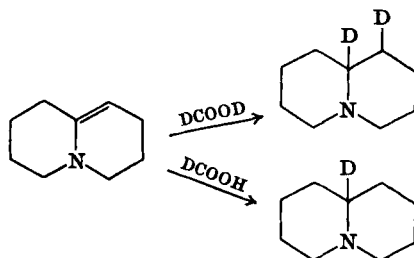
³⁰⁷ N. J. Leonard and R. C. Sentz, *J. Am. Chem. Soc.* **74**, 1704 (1952).

³⁰⁸ R. Lukeš, *Collection Czech. Chem. Commun.* **10**, 66 (1938).

³⁰⁹ P. L. DeBeneville and J. H. Macartney, *J. Am. Chem. Soc.* **72**, 3073 (1950).

³¹⁰ N. J. Leonard, P. D. Thomas, and V. W. Gash, *J. Am. Chem. Soc.* **77**, 1552 (1955).

plex unsaturated bases. Reduction of 1-methyl-2-alkyl- Δ^2 -piperideines (**93**) and analogous five-membered heterocyclic bases with formic acid has been studied by Lukeš *et al.*³¹¹⁻³¹³ The formic acid reduction has been used also in the synthesis of (+)-nicotine.¹²⁸ The formic acid reduction may be satisfactorily explained by the addition of a hydride ion or an equivalent particle to the α -carbon atom of the enamine.³¹⁴ This idea has been proved by the use of deuterated formic acid³¹⁵ (Scheme 13). Dienamines are reduced with formic acid partly in the 1,2- and partly in the 1,4-position.⁶⁰



SCHEME 13

The formic acid reduction has a great stereospecificity. Reduction of (–)- Δ^5 -dehydrosparteine (**94**) and (–)- $\Delta^{5,11}$ -didehydrosparteine (**96**) affords (–)-sparteine (**95**) and (–)- α -isoparteine (**97**),³¹⁰ respectively. In the reduction of these bases, the hydride ion approaches from the more accessible side of the molecule, i.e. from the side of the methylene bridge.

Reduction of the quaternary salt (**98**) obtained on treatment of 1-methyl-2-ethylidenepyrrolidine with ethyl bromoacetate leads to (–)-*erythro*-2-(2-N-methylpyrrolidyl)butyric acid (**99**),²²⁴ in agreement with Cram's rule.

Imines (2-alkyl- Δ^1 -piperideines and 2-alkyl- Δ^1 -pyrrolines) have been reduced by tin and hydrochloric acid, electrolytically, and by

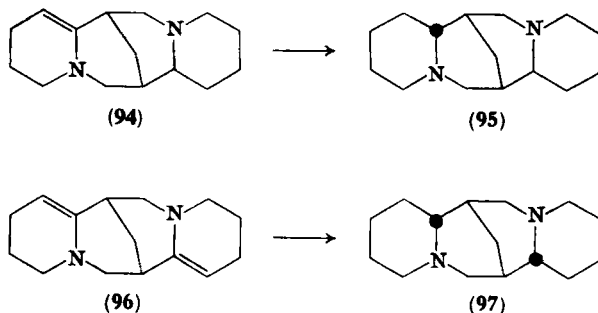
³¹¹ R. Lukeš and O. Červinka, *Chem. Listy* **51**, 2142 (1957); *Collection Czech. Chem. Commun.* **24**, 309 (1959).

³¹² R. Lukeš and O. Červinka, *Chem. Listy* **51**, 2086 (1957); *Collection Czech. Chem. Commun.* **23**, 1336 (1958).

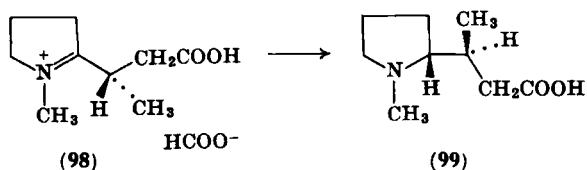
³¹³ R. Lukeš and V. Dědek, *Chem. Listy* **51**, 2082 (1957); *Collection Czech. Chem. Commun.* **23**, 2053 (1958).

³¹⁴ R. Lukeš and J. Jizba, *Chem. Listy* **47**, 1366 (1953); *Collection Czech. Chem. Commun.* **19**, 941 (1954).

³¹⁵ N. J. Leonard and R. R. Sauers, *J. Am. Chem. Soc.* **79**, 6210 (1957).

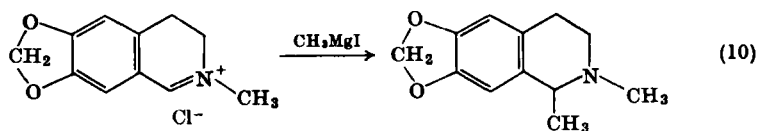


formic acid.³¹⁶ The reduction of 2-(4-pentenyl)- Δ^1 -piperideine with formic acid was accompanied by hydration of the isolated double bond.¹⁴⁹



The Wallach-Leuckart reductive alkylation of ammonia, and primary and secondary amines, by means of aldehydes and ketones, and the methylation of secondary amines according to Clarke and Eschweiler,^{316a} all possess a reduction step which is very similar to that observed in the reduction of enamines.³¹⁷

Organomagnesium compounds react with enamine salts to give bases substituted on the α -carbon atom. These reactions may be regarded as an extension of Freund's observations on quaternary quinolinium and isoquinolinium salts. The reaction of hydrastinine with methylmagnesium bromide³¹⁸ (Eq. 10) is a typical example. The



³¹⁶ R. Bonnett, V. M. Clark, A. Giddey, and A. Todd, *J. Chem. Soc.* 2087 (1959).

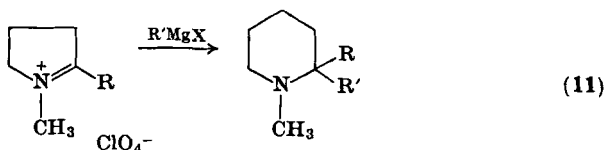
^{316a} M. L. Moore, *Org. Reactions* 5, 307 (1949).

³¹⁷ A. C. Cope, E. Ciganek, L. J. Fleckenstein, and M. A. P. Meisinger, *J. Am. Chem. Soc.* 82, 4651 (1960).

³¹⁸ M. Freund and K. Lederer, *Ber.* 44, 2356 (1911).

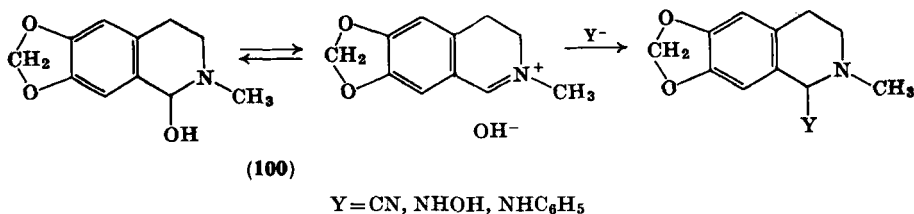
treatment of $\Delta^{5(10)}$ -dehydroquinolizidinium and $\Delta^{1(6)}$ -dehydrosparteinium perchlorates with alkylmagnesium halides has been studied by American authors.^{310, 319} In spite of the insolubility of these perchlorates in ether, good yields were obtained. The reaction course with the sparteine derivatives is again sterically directed so that only one diastereomer is formed.

Formation of α, α -disubstituted bases has been observed on treatment of 1-methyl-2-alkyl- Δ^2 -pyrrolinium perchlorates with alkylmagnesium halides³²⁰ (Eq. 11): satisfactory results were obtained only by using more polar solvents (ether-tetrahydrofuran or ether-pyridine).



Δ^1 -Pyrrolines and Δ^1 -piperideines react with Grignard reagents to yield merely an addition complex, which with water reforms the starting base.¹⁰ Further reaction occurs only with highly reactive organometallic reagents.³²¹ In some cases proton removal takes place and is followed by condensation with a second molecule of the Δ^1 -pyrroline.³¹⁶

Alkylolithium compounds and alkali cyanides, mercaptides, and alkoxides,^{322, 323} etc. have been used as nucleophilic reagents in reactions with the enamine salts. Nitrile groups can be removed by reduction or by treatment with acids. Treatment of cotarnine (100)



³¹⁹ K. Wiesner, Z. Valenta, A. J. Manson, and F. W. Stonner, *J. Am. Chem. Soc.* **77**, 675 (1955).

³²⁰ R. Lukeš, V. Dienstbierová, and O. Červinka, *Chem. Listy* **52**, 1137 (1958); *Collection Czech. Chem. Commun.* **24**, 428 (1959).

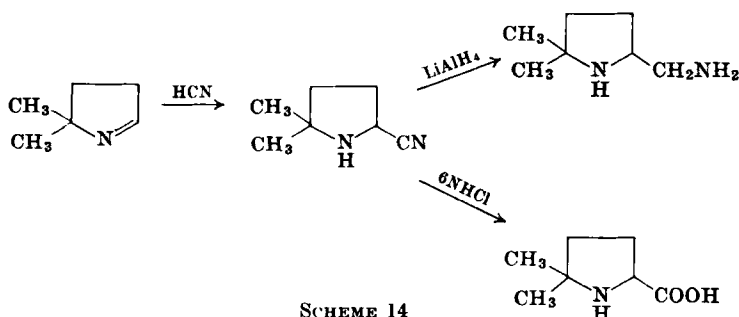
³²¹ R. Lukeš and M. Černý, *Collection Czech. Chem. Commun.* **26**, 2886 (1961).

³²² A. Kaufmann, *Ber.* **51**, 116 (1918); *J. Chem. Soc.* **114**, 187 (1918).

³²³ N. J. Leonard and A. S. Hay, *J. Am. Chem. Soc.* **78**, 1984 (1956).

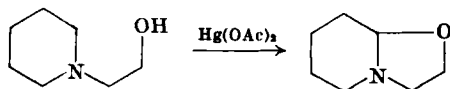
with hydrogen cyanide, hydroxylamine, and aniline has been reported.³²⁴

By contrast, addition of hydrogen cyanide to Δ^1 -pyrrolines yields stable nitriles, which are reduced by lithium aluminum hydride to diamines and can be saponified to acids³¹⁶ (Scheme 14).



SCHEME 14

Dialkylaminomethyl alkyl (and aryl) sulfides result from the treatment of α -halogeno-amines with mercaptans (thiophenols).³²⁵ Dehydrogenation of amino-alcohols with mercuric acetate^{182, 326} is accompanied by the intramolecular nucleophilic addition of the alkoxyl group when formation of a five- or six-membered ring is possible, e.g.:



Diazomethane reacts with the salts of enamines to yield aziridinium salts.^{327, 327a} Thus *N*-cyclohexylidenepyrrolidinium perchlorate yields 2,2-pentamethylene-1,1-tetramethyleneaziridinium perchlorate (**101**). Hydrogenation over Adams catalyst cleaves the bond between the quaternary nitrogen atom and the methylene group to form *N*-(1-methylecyclohexyl)pyrrolidinium perchlorate (**102**).

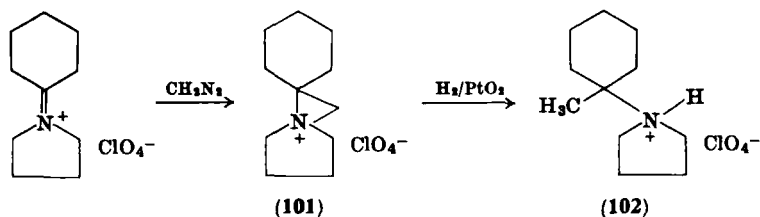
³²⁴ D. Béke, C. Szantay, and M. Bárczai-Béke, *Ann. Chem.* **636**, 150 (1960).

³²⁵ H. Böhme and K. Hartke, *Chem. Ber.* **96**, 604 (1963).

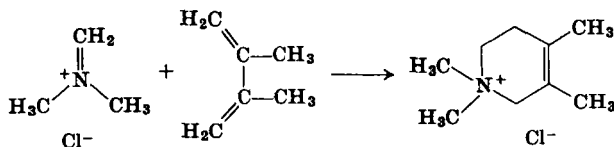
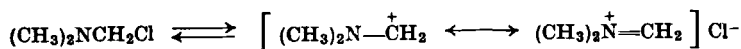
³²⁶ N. J. Leonard, K. Conrow, and R. R. Sauers, *J. Am. Chem. Soc.* **80**, 5185 (1958).

³²⁷ N. J. Leonard and K. Jann, *J. Am. Chem. Soc.* **82**, 6418 (1960); *ibid.* **84**, 4806 (1962).

^{327a} N. J. Leonard, K. Jann, J. V. Paukstelis, and C. K. Steinhardt, *J. Org. Chem.* **28**, 1499 (1963).



Diene addition³²⁸ occurs on treatment of dienes with α -halogenoamines (which are tautomers of enamine salts) (Scheme 15).



SCHEME 15

Triethylallylammonium chloride undergoes the Stevens rearrangement on treatment with phenyllithium.³²⁹ 2-Phenyl-3,3-dimethylindoline is rearranged to 2-phenyl-2,3-dimethylindoline by the action of phosphoric acid.³³⁰

Piperidylquinolizidines are obtained by ring-opening of $(-)\text{-}\Delta^{5,11}$ -didehydrosparteine with *tert*-butyl peroxide-cuprous chloride in pyridine, followed by reduction.³³¹

The *N*-oxides of Δ^1 -pyrrolines and Δ^1 -piperideines occupy a somewhat special position, although their reactions with nucleophilic reagents are similar to the reactions of other imines. These compounds have been studied particularly in connection with attempts to synthesize the cyclic skeleton corrin of vitamin B₁₂.

Reduction products of Δ^1 -pyrroline *N*-oxide vary according to the reducing agent used.¹¹¹ Sodium borohydride yields *N*-hydroxypyrrolidine. Reduction of 2,4,4-trimethyl- Δ^1 -pyrroline *N*-oxide (103)

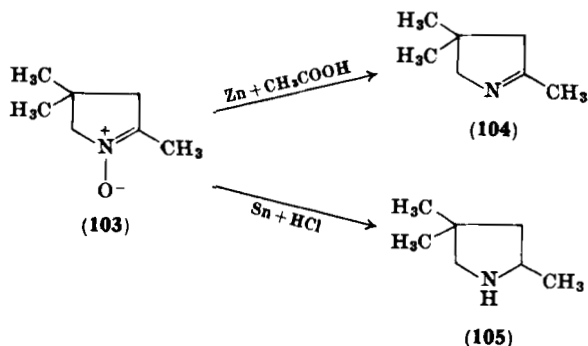
³²⁸ H. Böhme, K. Hartke, and A. Müller, *Chem. Ber.* **96**, 607 (1963).

³²⁹ H. Hellmann and G. M. Scheytt, *Ann. Chem.* **654**, 39 (1962).

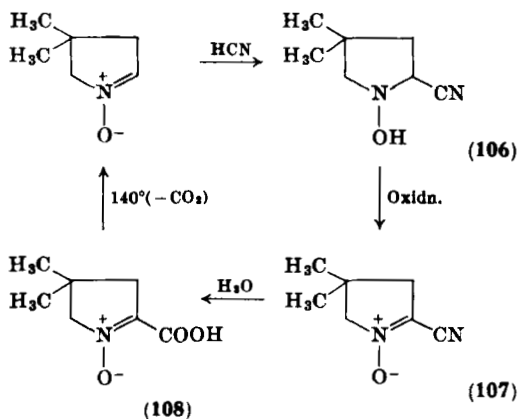
³³⁰ F. J. Evans and R. E. Lyle, *Chem. & Ind. (London)* p. 497 (1960).

³³¹ F. Bohlmann, E. Winterfeld, and G. Boroschewski, *Chem. Ber.* **93**, 1953 (1960).

with zinc and acetic acid affords 2,4,4-trimethyl- Δ^1 -pyrroline (**104**), whereas with tin and hydrochloric acid 2,4,4-trimethylpyrrolidine is obtained (**105**).



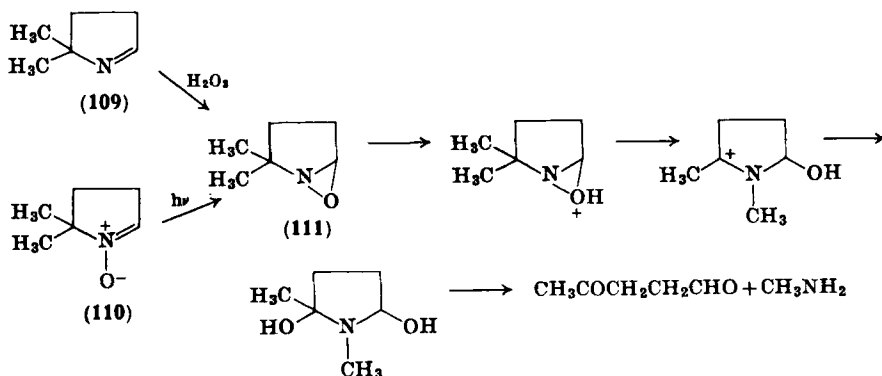
Δ^1 -Pyrroline *N*-oxides unsubstituted in the 2-position react readily with hydrogen cyanide to give 2-cyano-1-hydroxypyrrolidines (**106**), which undergo air oxidation to 2-cyano- Δ^1 -pyrroline *N*-oxides (**107**). Alkaline hydrolysis of the latter yields the corresponding acid (**108**).¹¹¹



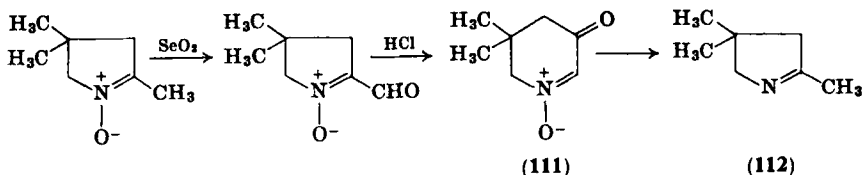
Oxidation of 5,5-dimethyl- Δ^1 -pyrroline (**109**) with hydrogen peroxide, or irradiation of the *N*-oxide (**110**), gave the bicyclic oxazirane **111**.^{332, 333} Thermal rearrangement of the oxazirane followed by hydrolysis yielded levulinic aldehyde.

³³² W. D. Emmons, *J. Am. Chem. Soc.* **78**, 6208 (1956).

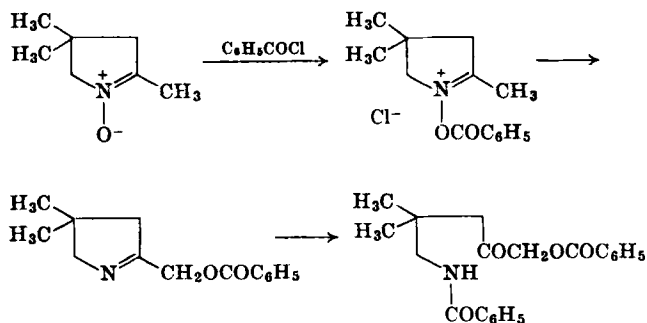
³³³ R. Bonnett, V. M. Clark, and A. Todd, *J. Chem. Soc.* p. 2102 (1959).



Oxidation of 2,4,4-trimethyl- Δ^1 -pyrroline *N*-oxide with selenium dioxide, followed by treatment with hydrogen chloride, causes ring-opening and reclosure to 2,3,4,5-tetrahydro-3,3-dimethyl-5-oxo-pyridine *N*-oxide (111). Clemmensen reduction of 111 forms 2,4,4-trimethyl- Δ^1 -pyrroline (112) by ring-contraction.³³⁴



Treatment of 2,4,4-trimethyl- Δ^1 -pyrroline *N*-oxide with benzoyl chloride is accompanied by ring-opening³³² (Scheme 16).

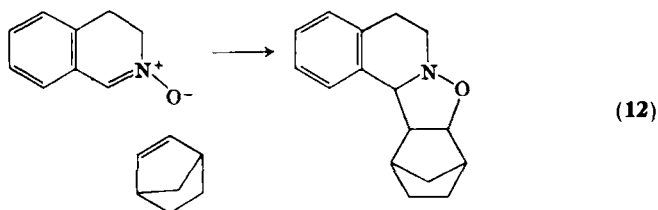


SCHEME 16

³³⁴ R. F. C. Brown, V. M. Clark, and A. Todd, *J. Chem. Soc.* p. 2105 (1959).

Δ^1 -Pyrroline *N*-oxides dimerize readily in alkaline media.³³⁵ Different products are obtained on treatment of 2,2-dimethyl- Δ^1 -pyrroline *N*-oxide with sodamide or triphenylmethyl sodium.³³⁶ Sodium-potassium alloy in ethylene glycol produces a derivative of 1,1'-dihydroxy-2,2'-dipyrrolidyl.³³⁷

Imine *N*-oxides are cyclic nitrones and undergo 1,3-cyclo-addition reactions³³⁸ (e.g. Eq. 12).



C. ALDOL REACTIONS OF ENAMINES

The aldol reactions of enamines may be formulated as reactions of the acyclic amino-aldehyde or amino-ketone form. However, at least with five- and six-membered heterocyclic enamines, the cyclic enamine forms take part in aldol reactions.

The simplest compounds, Δ^1 -pyrroline and Δ^1 -piperidine, are similar: both exist as trimers. Various products of the auto-condensation of Δ^1 -piperidine (**114**) have been described by Schöpf *et al.*,³³⁹ including two geometric isomers, α and β , of the trimer **113**. An equilibrium has been found to exist between Δ^1 -piperidine and the trimer which, therefore, reacts as a typical aldehyde-ammonia. The trimer rearranges spontaneously at pH 9–10 and 26° C in an almost quantitative yield to isotripiperidine (**115**)^{340, 341} which, in turn, is in equilibrium with tetrahydroanabasine (**116**) and Δ^1 -piperidine.³⁴⁰ Isotripiperidine contains a new C—C bond formed by an aldol

³³⁵ R. F. C. Brown, V. M. Clark, I. O. Sutherland, and A. Todd, *J. Chem. Soc.* p. 2109 (1959).

³³⁶ R. F. C. Brown, V. M. Clark, M. Lamchen, and A. Todd, *J. Chem. Soc.* p. 2116 (1959).

³³⁷ V. M. Clark, B. Sklarz, and A. Todd, *J. Chem. Soc.* p. 2123 (1959).

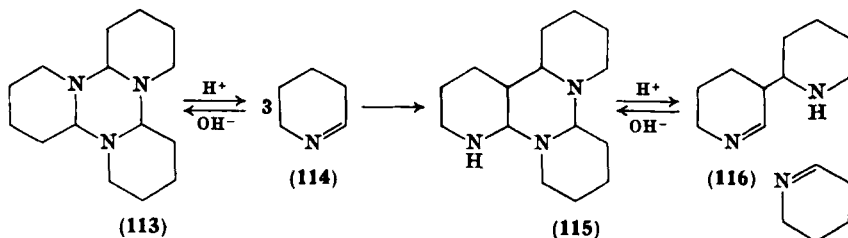
³³⁸ R. Grashey, R. Huisgen, and H. Leitermann, *Tetrahedron Letters* No. 12, 9 (1960).

³³⁹ C. Schöpf, A. Komzak, F. Braun, and E. Jacobi, *Ann. Chem.* **559**, 1 (1948).

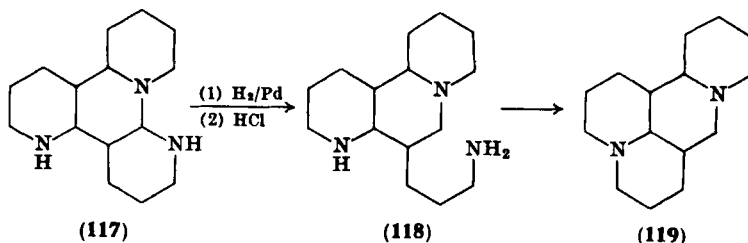
³⁴⁰ C. Schöpf, H. Arm, and F. Braun, *Chem. Ber.* **85**, 937 (1952).

³⁴¹ C. Schöpf, H. Arm, and H. Krimm, *Chem. Ber.* **84**, 690 (1951).

reaction. In aqueous media at pH 2–13, two molecules of Δ^1 -piperidine yield tetrahydroanabasine.



The so-called aldotripiperideine (117) is obtained by the action of acid catalysts on α -tripiperideine at its boiling point, or in aqueous solution at pH 9.2 and 100° C.^{342, 343} Further aldol reaction between tetrahydroanabasine and Δ^1 -piperidine obviously occurs. Hydrogenolysis of aldotripiperideine gives dihydroaldotripiperideine (118) which is convertible into matridine (119), a reduction product of the alkaloid matrine.³⁴³



Curiously, neither Δ^1 -piperidine nor tetrahydroanabasine undergo aldolization in strongly acidic or strongly basic media; reaction occurs only at pH 2–13.³³⁹ This relation between the rate of aldolization and pH indicates that aldolization occurs by condensation of the methylene group of the immonium salt with the free base.

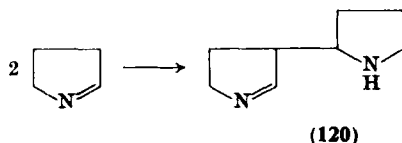
Δ^1 -Pyrroline affords a trimer, tripyrroline.³⁴⁴ Compounds analogous to isotripiperideine or aldotripiperideine have not yet been prepared in

³⁴² C. Schöpf, *Angew. Chem.* **62**, 452 (1950).

³⁴³ C. Schöpf, H. Arm, G. Benz, and H. Krimm, *Naturwissenschaften* **38**, 186 (1951).

³⁴⁴ A. Lüttringhaus, J. Jander, and R. Schneider, *Chem. Ber.* **92**, 1756 (1959).

the five-membered series; 3-(2-pyrrolidyl)- Δ^1 -pyrroline (120), a dimeric aldolization product, was always obtained.



Condensation of Δ^1 -pyrroline with pyrrole readily affords a stable compound, 2-(2-pyrrolidyl)pyrrole.⁹⁷ The pyrrole trimer^{345, 346} and indole dimer³⁴⁷ are formed by analogous aldol reactions. The dimerizations of some derivatives and analogs of Δ^1 -pyrroline and Δ^1 -piperidine, e.g. Δ^1 -pyrroline-2-carboxylic acid and 4-thia- Δ^1 -piperidine-2-carboxylic acid, take a similar course.³⁴⁸

The *N*-substituted bases also undergo aldolization when the 2-position is free. Reduction of *N*-substituted lactams and imides with various reducing reagents is accompanied by the formation of various amounts of unstable bases as by-products. Recently, it has been found that these by-products are formed on aldolization of intermediate 1-alkyl- Δ^2 -piperidines.¹⁷⁵ *N,N'*-Dimethyl- Δ^2 -tetrahydroanabasine is formed from 1-methyl-2-piperidone or *N*-methylglutarimide. The same dimer was obtained by Leonard and Hauck¹ on dehydrogenation of *N*-methylpiperidine with mercuric acetate, and by Schöpf *et al.*¹⁰¹ on partial hydrogenation of the *N*-methylpyridinium salts. The primary product in each of the above reactions, 1-methyl- Δ^2 -piperidine, exists only as the salt; the neutral species undergoes dimerization even in aqueous medium. Treatment of *N,N'*-dimethyl- Δ^2 -tetrahydroanabasine with acetonedicarboxylic acid affords *N*-methylisopelletierine. The reversibility of this aldolization reaction was established by Lukeš and Kovář,¹⁰⁵ Schöpf *et al.*,³⁴⁹ and Leonard and Cook.¹⁷⁵

Dimerizations of 1-alkyl- Δ^2 -pyrrolines have been studied to a lesser extent. The dimer of 1-methyl- Δ^2 -pyrroline was obtained by reduction of *N*-methylpyrrole with zinc and hydrochloric acid¹⁷⁶ and, together with the trimer, by mercuric acetate dehydrogenation of *N*-methyl-

³⁴⁵ A. Pieroni and A. Moggi, *Gazz. Chim. Ital.* **53I**, 120 (1923).

³⁴⁶ H. A. Potts and G. F. Smith, *J. Chem. Soc.* p. 4018 (1957).

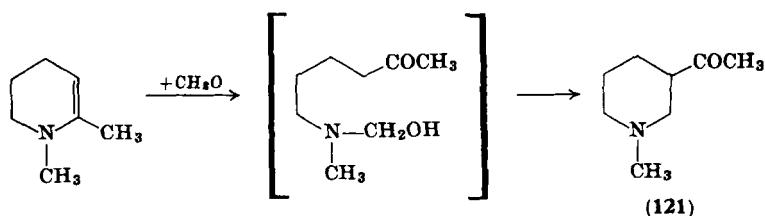
³⁴⁷ H. F. Hodson and G. F. Smith, *J. Chem. Soc.* p. 3544 (1957).

³⁴⁸ P. Hermann, *Chem. Ber.* **94**, 442 (1961).

³⁴⁹ C. Schöpf, R. Klug, and R. Rausch, *Ann. Chem.* **616**, 151 (1958).

pyrrolidine.¹⁷⁵ Interesting observations on the dimerization of Δ^1 -pyrroline *N*-oxides were reported by Todd *et al.*³³⁵

Moreover, a reaction of the Mannich type has been observed with heterocyclic enamines, e.g. in the treatment of 1,2-dimethyl- Δ^2 -piperidine with formaldehyde as described by Lipp and Widmann.³⁵⁰ In the condensation, the ring-opened form, *viz.* 1-methyl-amino-5-hexanone, is presumably involved. Recrystallization of the intermediate *N*-hydroxymethyl derivative then gives the final 1-methyl-3-acetylpiperidine (121).



Aldol reactions of enamines with reactive methylene groups constitute the basic step in the Robinson theory of alkaloid biogenesis.³⁵¹ The Mannich non-enzymic condensation of an aldehyde, ammonia (or a primary or secondary amine), and an active methylene compound occurs via an aldehyde-ammonia which is in equilibrium with other tautomeric forms (see Section II, A) under quasi-cellular conditions. Qualitative tests (e.g. condensation with *o*-aminobenzaldehyde to give a quinoxaline derivative^{339, 352}) established the presence of this unstable intermediate. The heterocyclic enamines Δ^1 -pyrroline and Δ^1 -piperidine and their *N*-methylated analogues are believed to originate from arginine and lysine,³⁵³ respectively, by metabolic conversions and to be precursors of pyrrolidine and piperidine alkaloids. Instead of an aldehyde, the corresponding α -keto-acid^{354, 355} may be involved; the α -keto-acid constitutes an intermediate stage in one possible reaction sequence for the degradation of an amino acid to an aldehyde. The following compounds may function as components in active methylene reactions: β -keto-acids,

³⁵⁰ A. Lipp and E. Widmann, *Ber.* **38**, 2471 (1905).

³⁵¹ R. Robinson, *J. Chem. Soc.* **111**, 876 (1917); 1079 (1936).

³⁵² C. Schöpf, *Angew. Chem.* **61**, 31 (1949).

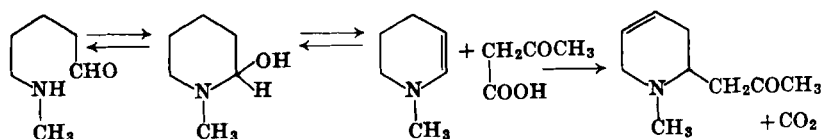
³⁵³ K. Mothes, *Pharmazie* **14**, 121 (1959).

³⁵⁴ G. Hahn and F. Rumpf, *Ber.* **71**, 2141 (1938).

³⁵⁵ L. Macholán, *Collection Czech. Chem. Commun.* **24**, 550 (1959).

additional (either identical or different) molecules of heterocyclic enamines, and reactive aromatic rings.

These biosynthetic processes have been studied *in vitro*³⁵⁶ with the aim of establishing the validity of biogenetic hypotheses and to find new routes for the synthesis of some pharmaceuticals.³⁵⁷ From a vast number of such reactions reported,³⁵⁸ the synthesis of *N*-methylisopelletierine¹⁰⁵ (Scheme 17), tetrahydroanabesine,^{352, 359} hygrine,^{360, 361} norhygrine,³⁶² isopelletierine,^{352, 363, 364} sedamine,³⁶⁵ nicotine,³⁵² adenocarpine,³⁶⁶ and sparteine³⁶⁷ may be quoted. Similar synthetic steps are postulated in more complicated biogenetic sequences such as those giving rise to the pyrrolizidine³⁶⁸ and lupinine alkaloids³⁶⁹ and annotine.³⁷⁰



SCHEME 17

The condensation of a heterocyclic enamine with *o*-aminobenzaldehyde, leading to the alkaloids of *Peganum harmala*, desoxyvasicine³⁷¹ and vasicine,³⁷² also include aldol-type reactions. The

³⁵⁶ C. Schöpf and G. Lehmann, *Ann. Chem.* **518**, 1 (1935).

³⁵⁷ E. Jucker, *Chimia (Aarau)* **9**, 195 (1955).

³⁵⁸ J. Trojáněk and K. Bláha, *Chem. Listy* **47**, 1682 (1953).

³⁵⁹ C. Schöpf, *Angew. Chem.* **59**, 29 (1947).

³⁶⁰ E. Anet, G. K. Hughes, and E. Ritchie, *Nature* **163**, 289 (1949).

³⁶¹ F. Galinovsky, A. Wagner, and R. Weiser, *Monatsh. Chem.* **82**, 551 (1951).

³⁶² M. Pailer, *Oesterr. Chemiker-Ztg.* **51**, 24 (1950).

³⁶³ C. Schöpf, F. Braun, K. Burkhardt, G. Dummer, and H. Müller, *Ann. Chem.* **626**, 123 (1959).

³⁶⁴ E. Anet, G. K. Hughes, and E. Ritchie, *Nature* **164**, 501 (1949); *Australian J. Sci. Research* **3A**, 336 (1950).

³⁶⁵ R. Lukeš, J. Kovář, K. Bláha, and J. Kloubek, *Collection Czech. Chem. Commun.* **21**, 1324 (1956).

³⁶⁶ C. Schöpf and K. Kreibich, *Naturwissenschaften* **41**, 335 (1954).

³⁶⁷ E. E. van Tamelen and R. L. Foltz, *J. Am. Chem. Soc.* **82**, 2400 (1960).

³⁶⁸ N. J. Leonard and S. W. Blum, *J. Am. Chem. Soc.* **82**, 503 (1960).

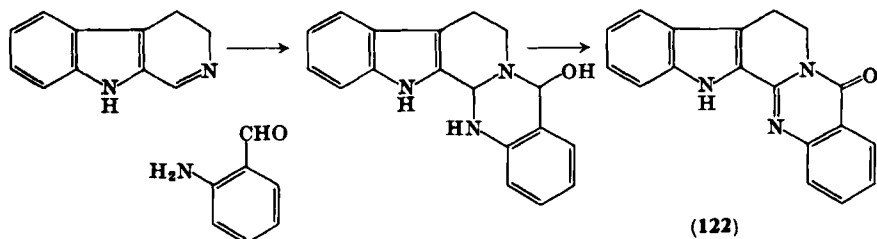
³⁶⁹ E. E. van Tamelen and R. L. Foltz, *J. Am. Chem. Soc.* **82**, 502 (1960).

³⁷⁰ E. Lecte, *Tetrahedron* **3**, 313 (1958).

³⁷¹ C. Schöpf and F. Oechler, *Ann. Chem.* **523**, 1 (1936).

³⁷² N. J. Leonard and M. J. Martell, *Tetrahedron Letters* No. 25, 44 (1960).

synthesis of rutaecarpine (**122**)³⁷³ starting with dihydronorharmane is similar in principle.



A characteristic of all the above reactions is that the yield depends on the pH,³⁷⁴ the maximum yield usually occurring near pH 7. Such reactions have been carried out *in vitro* in dilute aqueous buffer under so-called "physiological conditions," i.e. conditions attainable in the living cell. This over-simplified technique for the study of alkaloid biogenesis is now being abandoned in favor of experiments *in vivo* using labeled precursors,³⁷⁵ but such reactions are still of interest to organic chemists.³⁷⁶ The Robinson theory and the condensation reactions of heterocyclic enamines remain the starting point of all theories despite numerous modifications and additions.

D. SOME REACTIONS OF HETEROAROMATIC COMPOUNDS CONTAINING A FORMAL IMINE GROUP

1. Nucleophilic Reactions of Aromatic Heterocyclic Bases

Heterocyclic aromatic compounds containing a formal imine group (pyridine, quinoline, isoquinoline, and acridine) also react readily with nucleophilic reagents. A dihydro-derivative results, which is readily dehydrogenated to a new heteroaromatic system. Since the nucleophile always attacks the α -carbon atom, the reaction formally constitutes an addition to the C=N double bond. An actual localization of the C=N double bond in aromatic heterocyclic compounds is incompatible with molecular orbital theory. The attack of the nucleophilic reagent occurs at a site of low π -electron density, which is not

³⁷³ C. Schöpf and H. Steuer, *Ann. Chem.* **558**, 124 (1947).

³⁷⁴ C. Schöpf, *Angew. Chem.* **50**, 779 (1937).

³⁷⁵ W. O. James, in "The Alkaloids: Chemistry and Physiology" (R. H. F. Manske and H. E. Holmes, eds.), Vol. I. Academic Press, New York, 1950.

³⁷⁶ B. Franck, *Naturwissenschaften* **47**, 169 (1960).

necessarily the α -carbon but may be the γ - or (if available) ϵ -carbon atom.^{377, 378}

The decreasing reactivity of the most familiar aromatic heterocyclic compounds with nucleophilic reagents may be illustrated by the following sequence: quinoxaline > acridine > phenanthridine > isoquinoline > quinoline > pyridine. Acridine is alkylated in the 4-position, phenanthridine and quinoxaline in the α -position, isoquinoline in the 1-position, and quinoline and pyridine in the 2- or 4-positions. Weaker nucleophilic reagents seem to enter the 4-position of the pyridine and quinoline rings. If the addition occurs readily and in good yield, the intermediate dihydro derivative may sometimes be isolated; otherwise, the product of the subsequent oxidation results. In synthetic work the dihydro derivative is usually directly oxidized.

The Chichibabin reaction³⁷⁹ occurs in the α -position of the pyridine and quinoline rings and serves as an example. γ -Substitution occurs only if both α -positions are occupied. Reactions between aromatic nitrogen heterocycles and most organomagnesium compounds occur only under drastic conditions^{380, 381} and lead to α -alkylated products. More reactive Grignard reagents of the benzyl,³⁸² and especially of the allyl type,^{377, 383} react under milder conditions. Whereas the alkyl and aryl Grignard reagents react with pyridine to give 2-substituted derivatives,³⁸⁴ benzylmagnesium chloride yields a mixture of 4- and 2-benzylpyridine in a 3:1 ratio. Allylmagnesium chloride affords the 4-substituted derivative as the sole product. According to Gilman *et al.*,³⁷⁷ the activation energy of formation of the 1,4-dihydropyridine intermediates is lower than that of the 1,2-derivatives and, therefore, the first reaction prevails. With quinoline, the 2-position is preferred for the same reason (Scheme 18). Alkylation at the γ -position of the pyridine ring occurs more readily if one or two nitrile groups are present in the β -positions.³⁸⁵

³⁷⁷ H. Gilman, J. Eisch, and T. Soddy, *J. Am. Chem. Soc.* **79**, 1245 (1957).

³⁷⁸ H. C. Longuet-Higgins and C. A. Coulson, *Trans. Faraday Soc.* **43**, 87 (1947).

³⁷⁹ M. Ferles and J. Jizba, "Chemie pyridinu," p. 268. Nakladatelství ČSAV, Prague, 1957.

³⁸⁰ J. W. Bergstrom and S. H. McAllister, *J. Am. Chem. Soc.* **52**, 2845 (1930).

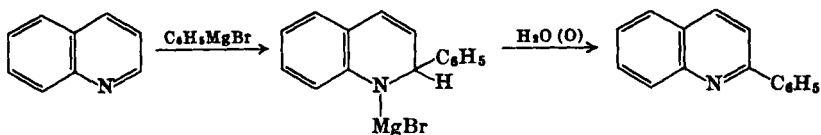
³⁸¹ K. Bláha, "Preparativní reakce v organické chemii VI. Reakce organokovových činidel," p. 508. Nakladatelství ČSAV, Prague, 1961.

³⁸² R. A. Benkeser and D. S. Holton, *J. Am. Chem. Soc.* **73**, 5861 (1951).

³⁸³ H. Gilman, J. Eisch, and T. S. Soddy, *J. Am. Chem. Soc.* **81**, 4000 (1959).

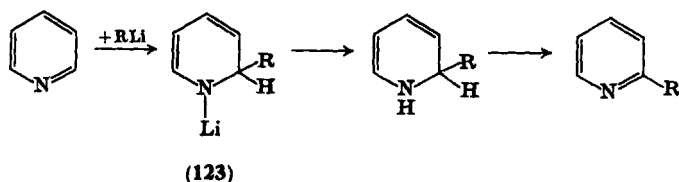
³⁸⁴ M. S. Kharasch and O. Reimuth, "Grignard Reactions of Nonmetallic Substances," p. 1251. Prentice Hall, Englewood Cliffs, New Jersey, 1954.

³⁸⁵ R. Lukeš and J. Kuthan, *Collection Czech. Chem. Commun.* **26**, 1422, 1845 (1961).



SCHEME 18

As reported by Ziegler and Zeiser,³⁸⁶ alkyl- or aryl-lithium compounds add very readily to pyridine. The unstable intermediate eliminates lithium hydride on heating and yields a 2-substituted pyridine. If the reaction mixture is decomposed without heating, an unstable dihydro derivative is obtained. The reaction course is analogous to that of the Chichibabin amination of pyridine with sodamide. Organolithium compounds also add to other heterocyclic compounds containing a pyridine ring. The intermediate addition products (123) are more stable with polycyclic bases than with pyridine itself. α -Substituted derivatives usually result, with the notable exception of acridines, where 1,4-addition occurs. With α -substituted quinolines, if the reaction is carried out at elevated temperatures, a second substituent is attached to the 2-position. Organolithium reagents also add to the α -position of quinoline if a halogen, alkoxy, or mercapto group is present in the 2-position. Compounds (2-picoline and quinaldine) containing a methyl group on the α -carbon atom form a heterocyclic lithium compound by substitution of a methyl hydrogen atom.



2. Reactions of Quaternary Salts of Aromatic Heterocyclic Bases with Nucleophilic Reagents

The quaternary salts of aromatic heterocyclic bases react with nucleophilic reagents much more readily than do the free tertiary bases. The increased reactivity reflects the immonium, as distinct

³⁸⁶ K. Ziegler and H. Zeiser, *Ber.* **63**, 1847 (1930); *Ann. Chem.* **485**, 174 (1931).

from the ammonium, structure of the starting compounds. The nucleophile usually attacks the same position as it does in the free bases.

Treatment of quaternary salts with alkali hydroxides affords pseudobases with an α -hydroxyl group. With α -alkylated pyridines a 2-hydroxyl derivative also results. The hydroxyl group of pseudobases derived from 3-substituted pyridines usually occurs in the 2-position, except for bulky or strongly electronegative β -substituents, when it occupies the 6-position. Treatment of *N*-alkylquinolinium salts with alkali hydroxide yields 1-alkyl-1,2-dihydro-2-hydroxyquinolines.³⁸⁷ Reaction occurs between quinoline and anhydrous hydrogen cyanide,²⁰² and an unstable quaternary salt is obtained from bromocyanogen and quinoline. The so-called Reissert compounds³⁸⁸ are formed from *N*-benzoylquinolinium chlorides and potassium cyanide. Other quaternary quinolinium salts react with alkali cyanides to yield 1-alkyl-4-cyano-1,4-dihydroquinolines.^{389, 390} Substitution in the 4-position occurs also with ethyl cyanoacetate³⁹¹ and other active methylene compounds.³⁹² *N*-Acylpyridinium salts also react in the 4-position.^{393, 394} Treatment of *N*-methoxypyridinium methosulfate with potassium cyanide yields 4-cyanopyridine.³⁹⁵

Freund, who first studied the reaction of heterocyclic quaternary salts with organomagnesium compounds, formulated the following rule³⁹⁶: If a compound which forms a pseudobase undergoes a Grignard reaction, the product formed carries the alkyl moiety of the Grignard reagent at the position of the hydroxyl group in the pseudobase. A dihydro derivative is again formed as an intermediate. α -Alkylation occurs, in contrast to the failure of less reactive nucleophilic agents, e.g. cyanide ion, to react. With quaternary pyridinium salts the Grignard reaction is relatively difficult,³⁹⁷ but quaternary

³⁸⁷ W. Bradley and S. Jeffrey, *J. Chem. Soc.* p. 2770 (1954).

³⁸⁸ A. Reissert, *Ber.* **38**, 1603, 3415 (1905).

³⁸⁹ A. Kaufmann and A. Albertini, *Ber.* **42**, 3776 (1909).

³⁹⁰ A. Kaufmann and A. Widmer, *Ber.* **44**, 2058 (1911).

³⁹¹ N. J. Leonard and R. L. Foster, *J. Am. Chem. Soc.* **74**, 2110 (1952).

³⁹² N. J. Leonard, H. A. De Walt, and G. W. Leubner, *J. Am. Chem. Soc.* **73**, 3325 (1951).

³⁹³ W. von E. Doering and W. E. McEwen, *J. Amer. Chem. Soc.* **73**, 2104 (1951).

³⁹⁴ E. Königs and E. Ruppelt, *Ann. Chem.* **509**, 142 (1934).

³⁹⁵ W. E. Feely and E. M. Beavers, *J. Am. Chem. Soc.* **81**, 4004 (1959).

³⁹⁶ M. Freund, *Ber.* **37**, 4666 (1944).

³⁹⁷ M. Freund and G. Bode, *Ber.* **42**, 1746 (1909).

salts of quinoline,³⁸⁷ isoquinoline,³⁹⁸ etc. react readily. A product has been isolated following treatment of the nicotine quaternary salt with methylmagnesium iodide.³⁹⁹ The yield is usually decreased if the alkyl group in the Grignard reagent is complex or bound to nitrogen. Alkylation in the 2-position is also effected by the action of Grignard reagents on pyridine *N*-oxide.⁴⁰⁰

The reaction of a Grignard reagent with quaternary salts obtained from *N*-oxides of pyridine, quinoline, and their homologs has been utilized^{401, 402} for the preparation of 2-alkylated compounds.

Reduction of aromatic heterocyclic bases and their quaternary salts is of particular interest. Reduction of pyridine with lithium aluminum hydride gives the unstable 1,2-dihydro derivative,⁴⁰³ whereas sodium in 95% ethanol yields 1,4-dihydropyridine. The latter is readily hydrolyzed with the formation of glutaric dialdehyde.⁴⁰⁴ Reduction of pyridine and its homologs with sodium in butanol affords a mixture of saturated and unsaturated bases; Δ^3 -piperideines are formed⁴⁰⁵ only from those pyridine homologs which possess alkyl groups in positions 3 and 4. Electrolytic reduction always gives a mixture of both bases.⁴⁰⁶ Δ^3 -Piperideines have been obtained by reduction with a mixture of lithium aluminum hydride and aluminum chloride.⁴⁰⁷

Reduction of quaternary salts of aromatic heterocyclic bases occurs much more readily. Quaternary salts of pyridine are reduced preponderantly to 1,2-dihydro derivatives⁴⁰⁸ with sodium amalgam and to 1,4-dihydro derivatives⁴⁰⁹ with sodium hydrosulfite. Potassium

³⁸⁸ M. Freund and G. Bode, *Ber.* **42**, 1758 (1909).

³⁹⁹ P. Karrer and A. Widmer, *Helv. Chim. Acta* **9**, 46 (1926).

⁴⁰⁰ E. Ochiai and K. Arima, *J. Pharm. Soc. Japan* **69**, 51 (1949); *Chem. Abstr.* **44**, 1502 (1950).

⁴⁰¹ O. Červinka, *Chem. & Ind. (London)* p. 1482 (1960); *Collection Czech. Chem. Commun.* **27**, 567 (1962).

⁴⁰² O. Červinka, A. Fábryová, and L. Matouchová, *Collection Czech. Chem. Commun.* **28**, 536 (1963).

⁴⁰³ F. Bohlmann, *Chem. Ber.* **85**, 390 (1952).

⁴⁰⁴ B. D. Shaw, *J. Chem. Soc.* **125**, 1930 (1924); **127**, 215 (1925).

⁴⁰⁵ M. Ferles, *Chem. Listy* **52**, 668 (1958); *Collection Czech. Chem. Commun.* **24**, 1029 (1959).

⁴⁰⁶ M. Ferles and M. Prystaš, *Collection Czech. Chem. Commun.* **24**, 3326 (1959).

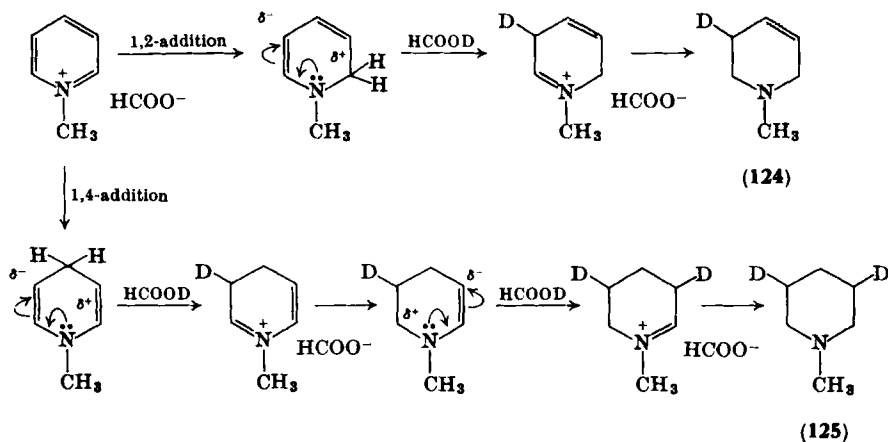
⁴⁰⁷ M. Ferles, *Sb. Vysoké Školy Chem. Technol. v Praze Oddíl. Fak. Anorg. Org. Technol.* **4**, part 2, 519 (1962).

⁴⁰⁸ P. Karrer, G. Schwarzenbach, and G. E. Utzinger, *Helv. Chim. Acta* **20**, 72 (1937).

⁴⁰⁹ K. Schenker and J. Druey, *Helv. Chim. Acta* **42**, 1960 (1959).

borohydride,⁴¹⁰ sodium borohydride,^{411, 412} lithium aluminum hydride,⁴¹³ and formic acid⁴¹⁴ are excellent reagents for the reduction of quaternary salts of aromatic heterocyclic bases.

Reduction of both the free bases and their quaternary salts proceeds by similar mechanisms. In pyridine and its quaternary salts, a hydride ion, or its equivalent, attacks a position of a low electron density, i.e. the 2- or 4-position. The mechanism of the reduction of quaternary salts of pyridine and its homologs (Lukeš and Ferles⁴¹⁴) has been elucidated using deuterated formic acid.⁴¹⁵ The hydride ion attack in position 2 is followed by addition of a proton to the enamine grouping with the formation of Δ^3 -piperideines (124). If the reduction commences with attack in the 4-position, a saturated base (125) is the final product. In agreement, α -picoline methobromide yields 1,2-dimethyl-1,2,3,6-tetrahydropyridine,³¹⁴ and β -picoline methobromide affords (presumably because of hyperconjugative stabilization) 1,3-dimethyl-1,2,5,6-tetrahydropyridine.⁴¹⁶



⁴¹⁰ J. J. Pahowse, *Compt. Rend.* **233**, 260, 1200 (1951).

⁴¹¹ K. Schenker, *Angew. Chem.* **72**, 638 (1960).

⁴¹² M. Ferles, *Chem. Listy* **51**, 474 (1957); *Collection Czech. Chem. Commun.* **23**, 479 (1958).

⁴¹³ M. Ferles, *Chem. Listy* **52**, 674 (1958); *Collection Czech. Chem. Commun.* **24**, 2221 (1959).

⁴¹⁴ R. Lukeš and M. Ferles, *Chem. Listy* **50**, 1471 (1956); *Collection Czech. Chem. Commun.* **22**, 121 (1957).

⁴¹⁵ O. Červinka and O. Kříž, *Collection Czech. Chem. Commun.* **30**, 1700 (1965).

⁴¹⁶ R. Lukeš and J. Pliml, *Collection Czech. Chem. Commun.* **15**, 463, 512 (1950).

Substitution in the Pyridine Series: Effect of Substituents

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I. Introduction—Scope and Limitations

This review concerns itself with the effects of substituents present in a pyridine nucleus upon the position and ease of attack at carbon by a suitable heterolytic or homolytic reagent. To this end, we shall limit ourselves to a consideration of the replacement of nuclear hydrogens: nucleophilic substitution of halogen atoms has already been discussed in this series by Illuminati in Volume 3, and by Shepherd and Fedrick in Volume 4, so that reference will be made to such reactions only where they permit a clearer understanding of the effects observed in the displacement of hydride ions. Reactions involving pyridine *N*-oxides and pyridinium salts will also be referred to briefly, but those of condensed ring systems such as quinoline and isoquinoline will only be considered in a few instances where they serve to illustrate a general point relative to the pyridines themselves. Quantitative results will be discussed whenever these are available—unfortunately, all too seldom. Finally, intramolecular cyclizations onto a pyridine ring will be treated briefly.

It has usually been assumed that the effects of substituents in the pyridine series parallel those in the benzene series. Although this is

often the case, it is by no means always so, and many reactions undergone by pyridine derivatives exhibit special features.

II. Theoretical Considerations

The behavior of pyridine, its *N*-oxide, and its quaternary salts has been the subject of a number of recent theoretical treatments.¹⁻⁴ The general conclusions will be summarized here to serve as a guideline on which to superimpose the effect of substituent groups.

Substitution of =N- for =CH- in benzene is accompanied by considerable deactivation toward electrophilic substitution, the effect being felt least at C-3 and most at C-2 and C-4. Both the π -electron density and the localization energy treatments agree on this point. It has been estimated⁵ that substitution of =N- is deactivating by a factor of at least 10^6 . Substitution of =NH^+ for a ring =CH- in benzene results in considerably greater deactivation of the nucleus toward electrophilic attack, with estimates varying from $<10^{-12}$ to 10^{-18} .^{3,5} π -Electron density calculations for the pyridinium ion predict, however, that the 2-, and not the 3-position, would have the highest electron-density,^{5a} which is contrary to the observed pattern of electrophilic substitution in the pyridinium ion. On the other hand, the atom localization energies correctly predict that C-3 should be the most easily substituted of the three positions by positive species. The choice as to whether the 2- or the 4-position will be attacked next (for example, if the pyridine ring bears two identical 3- and 5-substituents assumed, for the sake of argument, to exert the same influence at both C-2 and C-4) cannot be made on the basis of theoretical calculations carried out so far, since the predicted order of reactivity varies with the magnitude of the inductive parameter h chosen. The latest calculations suggest that substitution will take place at C-2.^{4b,c}

¹ R. A. Barnes, in "Pyridine and Its Derivatives" (E. Klingsberg, ed.), Pt. 1, Chapter I. Wiley (Interscience), New York, 1960.

² J. Eisch and H. Gilman, *Chem. Rev.* **57**, 525 (1957).

³ J. H. Ridd, in "Physical Methods in Heterocyclic Chemistry" (A. R. Katritzky, ed.), Vol. I, Chapter 2, p. 109. Academic Press, New York, 1963.

^{4a} G. Coppens and J. Nasielski, *Tetrahedron* **18**, 507 (1962).

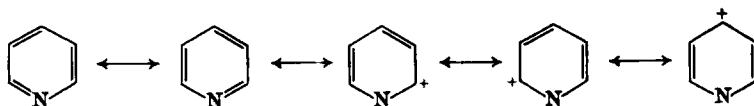
^{4b} R. Zahradník and C. Párkányi, *Collection Czech. Chem. Commun.* **30**, 355 (1965).

^{4c} A. H. Gawer and B. P. Dailey, *J. Chem. Phys.* **8**, 2658 (1965).

⁵ A. R. Katritzky and B. J. Ridgewell, *J. Chem. Soc.* **1963**, 3743.

^{5a} See however, reference 4^b.

The various theoretical approaches agree with the simple resonance theory representation of the valence structure of pyridine in predicting that nucleophilic substitution should take place readily at the 2-, 4-, or 6-positions but not at the 3- or the 5-position.



The pyridinium cation should be even more susceptible to nucleophilic attack. Again, differences of opinion exist as to whether the 2- or the 4-position should be more reactive, some calculations¹ indicating that attack at C-4 should occur more readily than at C-2, others^{3, 6} predicting exactly the opposite, depending not only upon whether one prefers to use ground state π -electron densities or atom localization energies for predictive purposes, but also upon the values of the parameters used in the calculations. It is important to remember that the lone-pair of electrons on the ring nitrogen atom cause it to complex with a very large variety of cations (free or otherwise) in solution, so that it may well be incorrect to consider calculations made for the free base as truly predictive of what could happen in individual reactions. One might suspect that since complexing at nitrogen—leading as it usually does to a lowering of the π -electron densities in the ring and of the nucleophilic atom localization energies—facilitates nucleophilic attack, then such substitution would always take place preferentially via the complexed pyridine molecule (factors such as back-donation of electrons must also be considered). That such an assumption is not *necessarily* correct is shown by the fact that, although the pyridine molecule should be very much more reactive toward electrophilic attack as the free base than as the protonated species, electrophilic proton exchange and nitration nevertheless take place via the pyridinium cation.^{5, 7a} Interestingly, while nitration of pyridine *N*-oxide appears to involve attack upon the free base,^{7b} acid-catalyzed hydrogen exchange proceeds *via* the conjugate acid.^{7c} Another point to bear in mind in nucleophilic aromatic substitutions in particular is

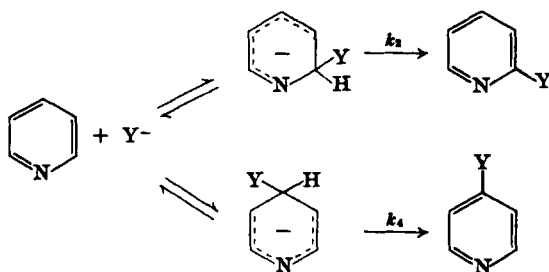
⁶ R. A. Barnes, *J. Am. Chem. Soc.* **81**, 1935 (1959).

^{7a} A. R. Katritzky and B. J. Ridgewell, *J. Chem. Soc.* **1963**, 3882.

^{7b} R. B. Moodie, K. Schofield, and M. J. Williamson, *Chem. Ind. (London)* **(1964)** 1577.

^{7c} A. R. Katritzky, B. J. Ridgewell, and A. M. White, *Chem. Ind. (London)* **(1964)** 1578.

that the loss of the hydride ion in the second stage of the reaction may well be rate-determining, so that if the first addition stage is readily reversible, the actual orientation observed may be quite different from the predicted mode of attack.^{4a, 8} This point will be discussed again later in the light of more recent experimental results.



The question of whether π -electron density or localization energy calculations should be used for predictive purposes has often been debated and is not within the scope of the present discussion. (It has recently been shown that the π -electron densities in the pyridinium cation vary with the nature of the counterion.^{8a}) We believe, however, that the most useful method will take into account the nature of the transition state in each individual case and consider not only the reactivity of the substrate itself but also the reactivity of the attacking reagent. Thus, with a very powerful reagent and a reactive substrate the transition state might be expected to resemble the ground state, with very little perturbation of the electronic distribution having occurred in reaching it (Hammond postulate). Under such circumstances, a correct assessment of the ground state π -electron densities should give a fairly accurate picture of the preferred positions of attack (assuming that factors such as steric effects, dipole-dipole attractions and repulsions, and other effects usually grouped under the heading of "ortho-effects" do not enter into the picture). On the other hand, with a weaker reagent or with a less reactive substrate the transition state will resemble a Wheland σ -complex and, under these circumstances, localization energy calculations should give a more accurate representation of the pattern of substitution. The use of total electron densities ($\sigma + \pi$), calculated by the extended Hückel Theory gives values which correlate quite well with experimental

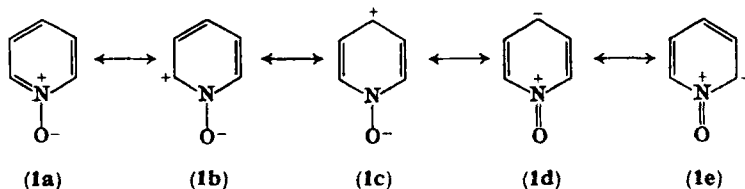
⁸ C. K. Ingold, "Structure and Mechanism in Organic Chemistry," p. 809. G. Bell, London, 1953.

^{8a} G. Kotowycz, T. Schaefer, and E. Bock, *Can. J. Chem.* **42**, 2541 (1964).

results.^{8b} Here the fact that the inductive effect along the σ -bonds of the ring N atom is felt more at C-2 than at C-4 is taken into account. Finally, the importance of solvation in determining orientation in heterolytic substitution has all too seldom been taken into consideration, though increasing attention is being devoted to it as an important, if not dominant, factor in determining relative reactivities.^{9, 10} The interesting frontier electron-density treatment,¹¹ which may be more directly applicable to charge-transfer complexing but would also be quite useful in a consideration of those cases where the transition state resembles the ground state, has been discussed from the point of view of heterolytic substitution.³

Both the atom localization energies for free-radical attack and the free-valence concept¹² have been used to predict the relative reactivities of the various nuclear positions toward homolytic attack. Both agree in proposing that the 2-position (which has the highest free valence and lowest value of A_r) will be attacked preferentially, but both predict partial rate factors slightly higher than those actually observed.¹³ A suitable choice of parameters ($\alpha_N = \alpha_C + \frac{1}{2}\beta$; $\beta_{CN} = \beta$) produced calculated reactivities based on atom localization energies which agree quite well with the experimentally observed rate factors.¹⁴ The predicted and observed order of reactivities in homolytic phenylation is $2 > 4 > 3$. No method available at present takes into account variations in the polarity of the attacking radical.^{15, 16}

Pyridine *N*-oxide is considered to be a resonance hybrid of various canonical structures (1a-e). Atom localization energies calculated



^{8b} W. Adam and A. Grimison, *Tetrahedron* **21**, 3417 (1965).

⁹ M. Liveris and J. Miller, *J. Chem. Soc.* **1963**, 3486.

¹⁰ R. A. Abramovitch, F. Helmer, and M. Liveris, Unpublished results (1965).

¹¹ K. Fukui, T. Yonezawa, C. Nagata, and H. Shingu, *J. Chem. Phys.* **22**, 1433 (1954).

¹² C. A. Coulson and C. Longuet-Higgins, *Proc. Roy. Soc. A* **192**, 16 (1947).

¹³ G. H. Williams, "Homolytic Aromatic Substitution," Chapter 2. Macmillan (Pergamon), New York, 1960.

¹⁴ R. D. Brown, *J. Chem. Soc.* **1956**, 272.

¹⁵ R. A. Abramovitch and J. G. Saha, *Tetrahedron Letters* **1963**, 301.

¹⁶ R. A. Abramovitch and J. G. Saha, *J. Chem. Soc.* **1964**, 2175.

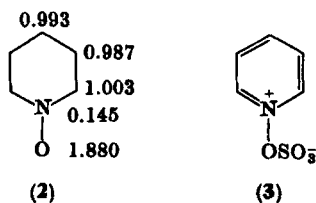
using 0.75β as the resonance integral of the N—O bond and 0.5β for the salt of pyridine *N*-oxide are given in Table I.⁶ The ground state π -electron densities at the various nuclear positions have been estimated to be as shown in 2.⁶ Both charge distribution and localization energy calculations predict that electrophilic substitution of the *N*-oxide should take place preferentially at the 2-position, whereas in

TABLE I
ATOM LOCALIZATION ENERGIES (IN UNITS OF β)^a

| | Pyridine- <i>N</i> -oxide | | | Salt of pyridine- <i>N</i> -oxide | | |
|-------|---------------------------|------|------|-----------------------------------|------|------|
| | 2 | 3 | 4 | 2 | 3 | 4 |
| A_e | 2.36 | 2.58 | 2.44 | 2.70 | 2.58 | 2.67 |
| A_r | 2.42 | 2.53 | 2.47 | 2.56 | 2.54 | 2.51 |
| A_n | 2.48 | 2.50 | 2.46 | 2.39 | 2.50 | 2.36 |

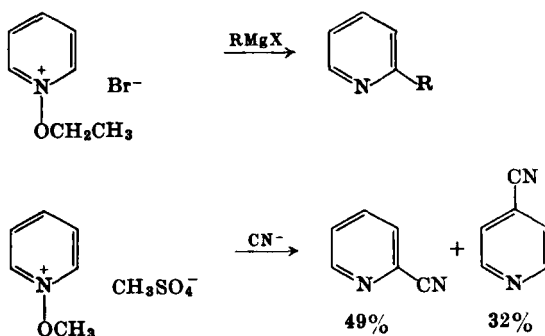
^a From Barnes.⁶

practice attack at the 4-position is usually observed. Thus, for example, nitration of pyridine *N*-oxide with nitric acid in sulfuric acid gives 4-nitropyridine *N*-oxide in high yield. Also, the conditions necessary to effect nitration are very much milder than those required to substitute pyridine itself. The observed orientation has been



attributed to steric hindrance by the oxide function to attack at C-2, and to the powerful adverse inductive effect of the positively charged nitrogen atom adjacent to the α -position. The steric effect of the oxygen atom upon the approaching electrophile can hardly be large enough to account for the almost complete lack of substitution at the α -position in, say, nitration. Other factors, such as the polarizability of the N—O group and solvation effects, may be of importance here.

Since sulfonation of pyridine *N*-oxide is about as difficult as is that of pyridine itself and takes place at the 3-position,¹⁷ it has been assumed¹⁸ that, in fuming sulfuric acid, pyridine *N*-oxide reacts only in the salt form (3), when the prediction is that substitution at C-3 would take place. It is, however, difficult to account for the fact that bromination, even at 110° in the presence of iron powder, does not occur.¹⁷ Bromination in chloroform solution in the presence of acetic anhydride and sodium acetate (when the *O*-acetate is the the probable substrate) take place readily, however, to give 3,5-dibromopyridine *N*-oxide.¹⁹ The predicted order of nucleophilic reactivity, on the basis of both atom localization energies and ground-state π -electron density calculations, is $4 > 2 > 3$.⁶ The same order is predicted for the nucleophilic substitution reactions of the salts of pyridine *N*-oxide. In actual practice, *N*-alkoxypyridinium derivatives undergo nucleophilic attack preferentially at C-2.²⁰⁻²³ The reaction of some pyridine *N*-oxides with phosphorus pentachloride may involve the formation



of a cyclic transition state leading to 2-chloropyridine,² although the production of 4-chloropyridines in many cases suggests the intervention of a nucleophilic attack by Cl⁻.

The foregoing brief discussion clearly indicates that, although some features of the substitution reactions of pyridine, pyridinium salts and

¹⁷ H. S. Mosher and F. J. Welch, *J. Am. Chem. Soc.* **77**, 2902 (1955).

¹⁸ A. R. Katritzky, *Quart. Rev.* **10**, 395 (1955).

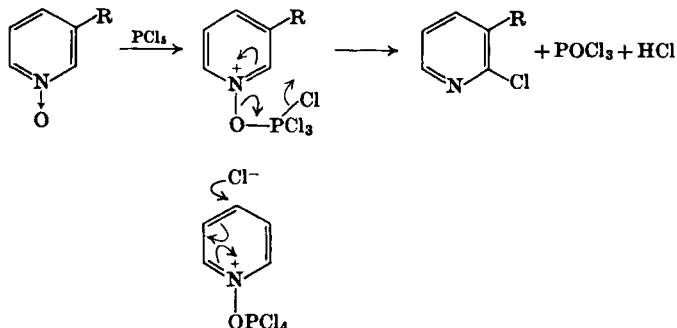
¹⁹ M. Hamana and M. Yamazaki, *Chem. Pharm. Bull. (Tokyo)* **9**, 414 (1961); *Chem. Abstr.* **55**, 24749 (1961); *J. Pharm. Soc. Japan* (1965), 62.

²⁰ O. Červinka, *Chem. Ind. (London)* **1960**, 1482.

²¹ H. Tani, *Yakugaku Zasshi* **81**, 141 (1961); *Chem. Abstr.* **55**, 14449 (1961).

²² W. E. Feely, G. Evanega, and E. M. Beavers, *Org. Syn.* **42**, 30 (1962).

²³ W. E. Feely and E. M. Beavers, *J. Am. Chem. Soc.* **81**, 4004 (1959).



pyridine *N*-oxide are accounted for *grosso modo* by current theories, these still lack the necessary flexibility required to explain the intimate details of orientation and reactivity in individual cases, in which differences in transition state geometries, rate-determining step, and solvation have to be considered explicitly.

III. Electrophilic Substitution

A. PYRIDINES AND PYRIDINIUM SALTS

Nuclear substitution of pyridine by electrophilic reagents usually requires very stringent conditions, conditions under which nitrobenzene undergoes polysubstitution. This is readily understood if it is assumed that, under the conditions of the reaction, the pyridine nitrogen is quaternized and that it is the pyridinium ion that is undergoing substitution. This assumption has been substantiated in the acid-catalyzed hydrogen exchange of 2,6-lutidine and 2,4,6-collidine⁵ and in the nitration of 2,4,6-collidine^{7a} and of quinoline.²⁴ If anything, *N*-methylpyridinium salts appear to nitrate more readily than the corresponding pyridines themselves,^{7a} which is as expected if nitration

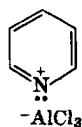
of pyridine involves attack on the pyridinium ion $=\text{NH}^+$: the electron-donating methyl group should then facilitate attack. Nitration of pyridine under homogeneous aprotic conditions has been attempted using a solution of nitronium borofluoride in sulfolane.^{24a} Only *N*-nitropyridinium ions were formed.

Many electrophilic substitution reactions of pyridine (such as sulfonation and chlorination) are catalyzed by salts such as mercuric

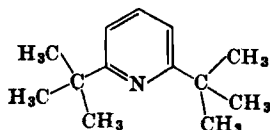
²⁴ M. V. Austin, M. Brickman, J. H. Ridd, and B. V. Smith, *Chem. Ind. (London)* **1962**, 1057.

^{24a} J. Jones and J. Jones, *Tetrahedron Letters*, **1964**, 2117.

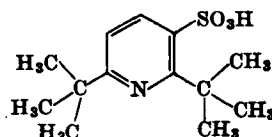
sulfate and aluminum chloride. Coordination of the metal ion to the ring-nitrogen atom is undoubtedly involved here, e.g. **4**,²⁵ back-donation of electrons from the metal probably occurring to decrease the formal positive charge on nitrogen and hence in the ring as a whole.¹ Striking confirmation of the strongly deactivating influence



(4)



(5)



(6)

that results from coordination at the ring nitrogen is seen in the ease with which 2,6-di-*t*-butylpyridine (**5**) undergoes sulfonation with sulfur trioxide in liquid sulfur dioxide at -10° to give the 3-sulfonic acid (**6**).^{26, 27} Steric hindrance prevents coordination at nitrogen in **5** so that substitution of the free base can take place.

1. Alkylpyridines

Alkyl substituents activate the nucleus toward nitration (with potassium nitrate in fuming sulfuric acid). 2-Picoline is nitrated at 160° to give a low (3.6%) yield of a mixture of 3- and 5-nitro-2-picoline.²⁸ The isomer ratio was not determined and it would be interesting to do so. The introduction of a second methyl group causes a marked increase in the reactivity of the nucleus, for 2,6-lutidine is mononitrated in 66–80% yield at 100° to give the 3-nitro-compound. Under these conditions a 90% yield of 3-nitro-2,4,6-collidine is obtained from *sym*-collidine.^{28, 29} That the 2,6-dimethyl groups are not exerting a steric effect inhibiting protonation of the ring nitrogen atom (i.e., that nitration of the =NH^+ species is occurring, and not of the free base in equilibrium with the pyridinium ion) has already been mentioned.^{7a} Nitration of 2,4-lutidine gives a mixture of

²⁵ D. E. Pearson, W. W. Hargrove, J. K. T. Chow, and B. R. Suthers, *J. Org. Chem.* **26**, 789 (1961).

²⁶ H. C. van der Plas and H. J. den Hertog, *Tetrahedron Letters*, **1960**, 13.

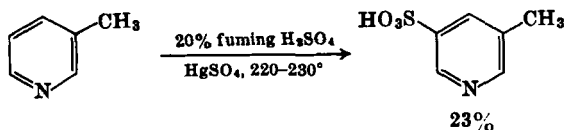
²⁷ H. C. Brown and B. Kanner, *J. Am. Chem. Soc.* **75**, 3865 (1953).

²⁸ E. Plazek, *Ber.* **72**, 577 (1939).

²⁹ E. V. Brown and R. H. Neil, *J. Org. Chem.* **26**, 3546 (1961).

about equal amounts of the 3- and the 5-nitro derivatives.^{29a} The orientation observed in the above examples is that imposed by the combined directive influences of the ring nitrogen atom and of the methyl groups. It might be of interest to study the nitration of 3,5-lutidine or of 2,3,4-collidine.

At first glance, the mercuric ion-catalyzed sulfonation of pyridine homologs appears to present a reversal of the trend observed in nitration. A comparison of the sulfonation of pyridine and the picolines with fuming sulfuric acid indicated lower yields from 2-picoline³⁰ and 4-picoline^{30, 31} than from pyridine itself and still lower yields from 3-picoline.³⁰ The decreased yields with the picolines have been attributed to tar formation accompanying oxidation of the alkyl groups by the sulfuric acid.³⁰ The reported formation of 5-ethyl-2-methylpyridine-3-sulfonic acid from 5-ethyl-2-methylpyridine³²⁻³⁴ could not be reproduced.³⁵ The main product isolated from the sulfonation of 2-picoline was the 5-sulfonic acid, identified by its conversion in low yield into the corresponding nitrile³⁰ and phenol.³⁶ No attack at C-3 was reported but, in view of the method of analysis used, some 3-sulfonic acid may have been formed but not identified. The dominating orienting influence of the ring nitrogen atom is maintained in 3-picoline, from the sulfonation of which only 3-methylpyridine-5-sulfonic acid was isolated.³⁰ In 4-picoline, in which the orienting influences of the methyl group and ring nitrogen atom reinforce each other, the 3-sulfonic acid is also obtained as expected.³⁰ When 2,6-di-*t*-butylpyridine is sulfonated with sulfur trioxide in a



^{29a} L. Achremowicz, T. Batkowski, and Z. Skrowaczewska, *Roczniki Chem.* **38**, 1317 (1964).

³⁰ S. M. McElvain and M. A. Goese, *J. Am. Chem. Soc.* **65**, 2233 (1943).

³¹ J. L. Webb and A. H. Corwin, *J. Am. Chem. Soc.* **66**, 1456 (1944).

³² I. G. Farbenindustrie A.-G., French Patent 685,062; *Chem. Abstr.* **24**, 5307 (1930).

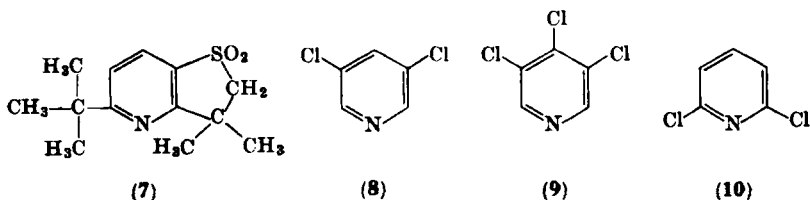
³³ O. Wulff, German Patent 541,036; *Chem. Abstr.* **26**, 1945 (1932).

³⁴ O. Wulff, U.S. Patent 1,880,646; *Chem. Abstr.* **27**, 515 (1933).

³⁵ L. E. Tenenbaum, in "Pyridine and Its Derivatives" (E. Klingsberg, ed.), Pt. 2, Chapter 5, p. 155. Wiley (Interscience), New York, 1961.

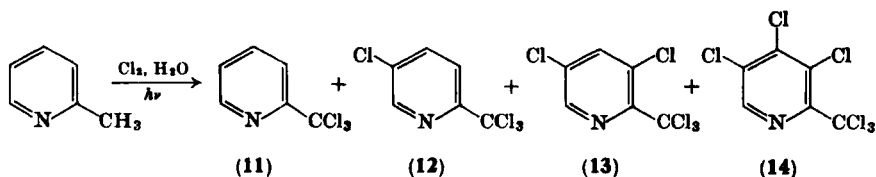
³⁶ T. Urbański, *J. Chem. Soc.* **1947**, 132.

sealed tube at 240–250° there is obtained, in addition to compound **6** (30–35%), a 15–20% yield of 2,3-dihydro-3,3-dimethyl-5-*t*-butylthieno[3,2-*b*]pyridine 1-dioxide (**7**).³⁷



Orientation in the halogenation of pyridine and its homologs is complicated by the possible intervention of different mechanistic pathways while using the same halogenating agent. Chlorination of pyridine in the gas phase, for example, is thought to proceed by either an electrophilic or a homolytic mode of attack, depending on the temperature at which the reaction is carried out.^{38, 39} At 200°, electrophilic attack leads to the formation of 3,5-dichloro- (**8**) and 3,4,5-trichloropyridine (**9**), the latter presumably arising from the chlorination of **8**. At 270°, 2-chloropyridine is the main product, together with the product of further substitution, 2,6-dichloropyridine (**10**). The latter is the main product (together with extensive carbonization) when the reaction is carried out at 400°. At the higher temperatures the active reagents are probably chlorine atoms (see Section V).

The light-catalyzed chlorination of 2-picoline with chlorine water is said to involve substitution of the side-chain first, to give 2-trichloromethylpyridine (**11**) which, under more vigorous conditions, gives the 5-chloro (**12**), the 3,5-dichloro (**13**), and the 3,4,5-trichloro, derivatives (**14**).⁴⁰ The side-chain chlorination may well be a homolytic process,



³⁷ H. C. van der Plas and T. H. Crawford, *J. Org. Chem.* **26**, 2611 (1961).

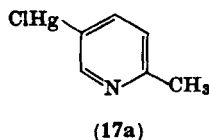
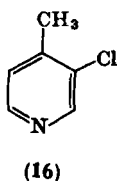
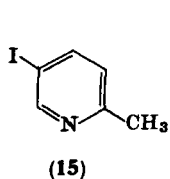
³⁸ J. P. Wibaut and J. R. Nicolai, *Rec. Trav. Chim.* **58**, 709 (1939).

³⁹ Z. Rodewald and E. Plazek, *Roczniki Chem.* **18**, 39 (1938).

⁴⁰ E. T. McBee, H. B. Hass, and E. M. Hodnett, *Ind. Eng. Chem.* **39**, 389 (1947).

whereas attack at C-5 indicates a heterolytic mechanism for the nuclear substitution. Under the same conditions, apparently no chlorinated products could be isolated from 3- and 4-picoline.

When 2-picoline hydrochloride was heated for 15 hours at 120–130° with bromine, a monobromopicoline was isolated but the position of the bromine atom was not determined.⁴¹ Iodination of 2-picoline with iodine in oleum at 300–320° is reported to give 5-iodo-2-picoline (**15**),⁴² the *para*-directive influence of the 2-methyl group being similar to that observed in sulfonation (and perhaps also nitration). Under the same conditions, 4-picoline gives the expected 3-iodo-4-picoline, together with a low yield of 3,5-diiodo-4-picoline.⁴³ Iodination of 2,6-lutidine to give 3-iodo-2,6-dimethylpyridine is effected in 30% oleum at 200°.⁴⁴ 2,4,6-Collidine is iodinated under milder conditions (an acid with a lower SO₃ content may be used) and the yield of product (containing considerable amounts of the 3,5-diiodo derivative) is higher.⁴³ The so-called swamping catalyst effect, in which pyridine and its methyl



derivatives are chlorinated or brominated under relatively mild conditions (80–100°) in the presence of an excess of aluminum chloride is thought to involve attack by a highly polarized (and hence more reactive) halogen molecule upon the pyridine–aluminum chloride complex, e.g. **4**.²⁵ Chlorination of 4-picoline gives 3-chloro-4-picoline (**16**) (40%) and 3,5-dichloro-4-picoline (15%). Bromination gave a 32% yield of 3-bromo-4-picoline, with no product of attack at C-2 detected. Bromination of 2-picoline gave a mixture of 3-bromo- and 5-bromo-2-picoline (40% yield) from which only the latter could be isolated in a pure form in 6.5% yield. The isomer ratio was not determined. Bromination of 3-picoline in the presence of excess aluminum

⁴¹ S. M. McElvain and M. A. Goese, *J. Am. Chem. Soc.* **65**, 2227 (1943).

⁴² E. Plazek and Z. Rodewald, *Roczniki Chem.* **21**, 150 (1947); *Chem. Abstr.* **42**, 5456 (1948).

⁴³ E. Plazek, K. Dohaniuk, and Z. Grzyb, *Roczniki Chem.* **26**, 106 (1952).

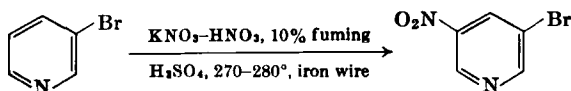
⁴⁴ T. Batkowski and E. Plazek, *Roczniki Chem.* **25**, 251 (1951).

chloride gave a mixture which was resolved by gas chromatography into three components; the main product formed is 5-bromo-3-picoline.⁴⁵ Bromination of 3-picoline in the presence of thionyl chloride gave a mixture containing four products.⁴⁶

Mercuration of 2-picoline with mercuric acetate followed by treatment with sodium chloride gave 5-chloromercuri-2-picoline (**17a**),⁴⁷ the ease of substitution being greater than with pyridine itself. 4-Picoline gave 4-methyl-3-pyridylmercuric acetate.⁴⁸

2. Halogenated Pyridines

No quantitative data are available about whether halogen substituents deactivate the pyridine nucleus toward electrophilic attack. That the normal *o*:*p*-directing influence of a halogen atom is less powerful than the *m*-directing one of the pyridine ring nitrogen atom is readily discerned. Thus, nitration of 3-bromopyridine with potassium nitrate and nitric acid in 10% fuming sulfuric acid at 270–280° in the presence of iron wire gave a 7% yield of 5-nitro-3-bromopyridine.⁴⁹ The yield was lower if the iron was left out. Nitration of 3-chloro- and 3-iodopyridine gave comparably low yields of the 5-nitro derivatives but in these cases the addition of iron wire was without influence upon the yields of products.⁴⁹ As previously mentioned, the gas-phase chlorination of 3-chloropyridine at 200° gave



3,5-dichloropyridine³⁹ together with some 3,4,5-trichloropyridine.³⁸ Bromination of 3-bromopyridine at 300° gives mainly 3,5-dibromopyridine together with very small amounts of 3,4-dibromopyridine (**17b**) and trace amounts of 2,5- (**18**) and 2,3-dibromopyridine (**19**).^{50, 51}

⁴⁵ R. A. Abramovitch and M. Saha, Unpublished results (1965).

⁴⁶ E. E. Garcia, C. V. Greco, and I. M. Hunsberger, *J. Am. Chem. Soc.* **82**, 4430 (1960).

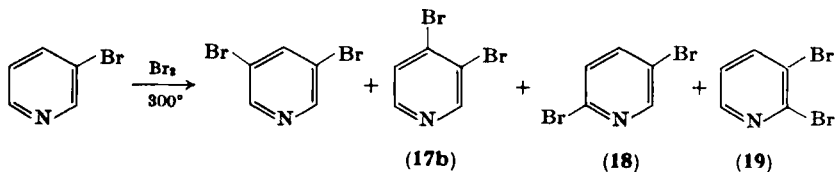
⁴⁷ M. W. Swaney, M. J. Skeeters, and R. N. Shreve, *Ind. Eng. Chem.* **32**, 360 (1940).

⁴⁸ G. R. Clemo and G. A. Swan, *J. Chem. Soc.* **1948**, 198.

⁴⁹ E. Plazek, A. Sorokowska, and D. Tolopka, *Atti 10. Congr. Intern. Chim. Rome*, 1938 Vol. III, p. 290; *Roczniki Chem.* **18**, 210 (1938).

⁵⁰ H. J. den Hertog and J. P. Wibaut, *Rec. Trav. Chim.* **51**, 940 (1932).

⁵¹ H. J. den Hertog, *Rec. Trav. Chim.* **64**, 85 (1945).



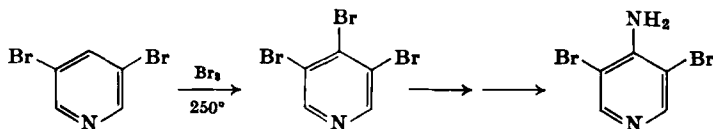
At higher temperatures (500°), as in the case of chlorination, homolytic attack by bromine atoms takes place. Bromination of pyridine hydrochloride under pressure or of pyridine in 90% sulfuric acid in the presence of silver sulfate gives a very low yield of equal amounts of 3-bromopyridine and 3,5-dibromopyridine (the latter arising from further bromination of the former, probably as the protonated form).^{52, 53} On the other hand, the bromination of pyridine in 65% fuming sulfuric acid at 130° with insufficient bromine gives, as the main product, 3-bromopyridine, together with small amounts of dibromopyridines in which the 2,5-isomer was found to predominate (gas chromatographic analysis), with 3,5- and 2,3-dibromopyridine formed in lower yields.⁵³ It is suggested that in fuming sulfuric acid Br^+ is present in fair amount and that it is the 3-bromopyridine- SO_3 complex (which, being overall electrically neutral, should be less deactivated than the 3-bromopyridinium ion) which is undergoing further substitution. Under these conditions it is apparent that the *para*-directing influence of the bromine atom overrides to a major extent the *meta*-directing influence of the $\equiv \text{N}^+-\text{SO}_3^-$ group.

The bromination of mono- and dibromopyridines at 300° in the presence of pumice impregnated with ferrous bromide or zinc bromide takes place by electrophilic attack of the substrate. If the pumice is impregnated with cuprous bromide, homolytic substitution appears to take place, since the observed orientation is characteristic of the latter mode of attack. Thus, 2-bromopyridine with pumice- FeBr_2 as the contact substance is brominated first to 2,5-dibromopyridine which, in turn, gives 2,3,5-tribromopyridine.⁵⁰ No 2,3-dibromopyridine could be detected, so that the bromine substituent originally present apparently orients the first entering group *para*. Similarly, 2,6-dibromopyridine gives 2,3,6-tribromopyridine, which is further brominated to 2,3,5,6-tetrabromopyridine. The vapor-phase bromination of pyridine at 250° gives, in addition to 3,5-dibromopyridine,

⁵² A. W. Hofmann, *Ber.* **12**, 988 (1879).

⁵³ H. J. den Hertog, L. van der Does, and C. A. Landheer, *Rec. Trav. Chim.* **81**, 864 (1962).

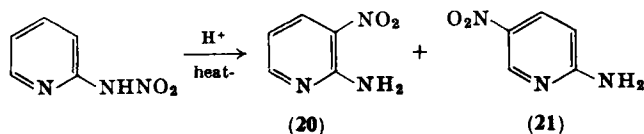
3,4,5-tribromopyridine, which reacts with pyridine to give a pyridinium salt. Hydrolysis of the latter gives 4-amino-3,5-dibromopyridine.⁵⁰ The 3- and 5-bromine substituents thus direct the entering bromine to the vacant position between them, as has already been



seen in the chlorination of **8** to give **9**.³⁸ Iodination of 3-iodopyridine with iodine in fuming sulfuric acid at 300–320° gives 3,5-diiodopyridine.^{53a}

3. Aminopyridines

As expected, the strongly activating and *ortho-para* directing amino group greatly facilitates electrophilic attack upon any pyridine nucleus to which it is attached and, in fact, exerts the dominating orienting effect, even when the ring bears a strongly deactivating substituent. Nitration of 2-aminopyridine proceeds in two distinct steps: the first, the formation of 2-*N*-nitraminopyridine, is followed on warming by an exothermic rearrangement to give a mixture of 3-nitro- (**20**) and 5-nitro-2-aminopyridine (**21**) in the ratio of 1:8. The



2,3-:2,5- isomer ratio is somewhat higher when the rearrangement is carried out at a higher temperature.^{54–56} The amino group is clearly predominantly *para*-directing in this reaction. It has recently been proposed that the acid-catalyzed nitramine rearrangement involves free-radical intermediates^{57, 58} so that this reaction may, in fact, have to be considered under a heading different from that of electrophilic

^{53a} Z. Rodewald and E. Plazek, *Ber.* **90**, 1159 (1957).

⁵⁴ A. E. Tschitschibabin and B. A. Rasorenov, *J. Russ. Phys. Chem. Soc.* **47**, 1286 (1915); *Chem. Zentr.* **94** (part III), 1025 (1923).

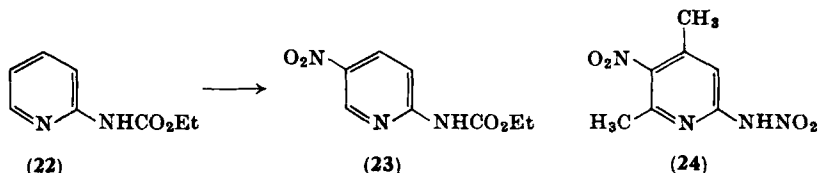
⁵⁵ F. Korte, *Ber.* **85**, 1012 (1952).

⁵⁶ L. N. Pino and W. S. Zehring, *J. Am. Chem. Soc.* **77**, 3154 (1955).

⁵⁷ W. N. White and J. T. Golden, *Chem. Ind. (London)* **1962**, 138.

⁵⁸ W. N. White, D. Lazdins, and H. S. White, *J. Am. Chem. Soc.* **86**, 1517 (1964).

substitutions once the mechanism has been firmly established. On the other hand, a study of the rearrangement of 2-nitraminopyridine in sulfuric acid in the presence of $\text{Na}^{15}\text{NO}_3$ has led to the suggestion that this rearrangement is intramolecular in character, the observed entry of a small amount of ^{15}N into the nucleus being explainable on the basis of an exchange between the nitraminopyridine nitro group and $^{15}\text{NO}_2^+$.⁵⁹ 2-Dimethylaminopyridine, which cannot form a nitramino derivative, is nitrated in high yield to give a mixture of 3-nitro and 5-nitro-2-dimethylaminopyridine in the ratio of 1:9.^{60, 61} Nitration of 2-dimethylaminopyridine *N*-oxide under vigorous conditions gives 2-dimethylamino-5-nitropyridine, loss of the side-chain *N*-oxide grouping accompanying nitration.⁶² Nitration of 2-acetamidopyridine is preceded by deacetylation,⁶³ but that of ethyl 2-pyridylcarbamate (22) gives a 46% yield of the 5-nitro derivative 23.⁶⁴ 2-Amino-4,6-dimethylpyridine gave 2-nitramino-5-nitro-4,6-dimethylpyridine (24),



no 3-nitro isomer being isolated,⁶⁵ whereas 6-amino-5-ethyl-2-picoline gave a mixture of 6-amino-5-ethyl-3-nitro-2-picoline and 6-nitramino-5-ethyl-2-picoline. Surprisingly, warming the latter in sulfuric acid failed to effect the expected rearrangement.⁶⁶ Rearrangement of the nitramine from 2-methylaminopyridine gives a 1:10 ratio of the 3- and 5-nitro derivatives, respectively. The predominant formation of the product of *para*-substitution from the nitramine in all the above cases would tend to support the proposed intermolecular or partial intermolecular character for this rearrangement.^{57, 58}

If the 5-position is blocked, rearrangement to C-3 will take place,

⁵⁹ B. A. Geller and L. S. Samosvat, *Zh. Obshch. Khim.* **34**, 613 (1964); *Chem. Abstr.* **60**, 13112 (1964); *J. Gen. Chem. USSR* **2**, 614 (1964).

⁶⁰ A. E. Tschitschibabin and I. L. Knunjanz, *Ber.* **61**, 427 (1928).

⁶¹ A. E. Tschitschibabin and I. L. Knunjanz, *Ber.* **62**, 3053 (1929).

⁶² E. Plazek, Private communication (1964).

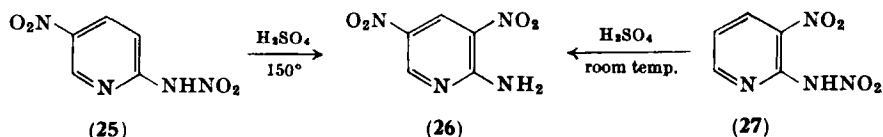
⁶³ E. Plazek and E. Sucharda, *Ber.* **61**, 1813 (1928).

⁶⁴ H. M. Curry and J. P. Mason, *J. Am. Chem. Soc.* **73**, 5043 (1951).

⁶⁵ A. Taurins and S. J. Viron, *Can. J. Chem.* **31**, 1048 (1953).

⁶⁶ A. E. Tschitschibabin and M. S. Widonowa, *J. Russ. Phys. Chem. Soc.* **53**, 238 (1921); *Chem. Zentr.* **94** (part III), 1025 (1923).

although not very readily in some cases. Thus, 2-amino-5-chloro^{67, 68} and the corresponding 5-bromopyridine^{69, 70} give the 3-nitro derivatives readily, whereas the 2-nitramino-5-iodopyridine is said not to undergo isomerization.⁷¹ A carboxyl group *para* to the amino group deactivates the nucleus sufficiently that it requires heating with sulfuric acid at 100° for 15 hours to rearrange 6-nitraminonicotinic acid to 6-amino-5-nitronicotinic acid.⁷² No difficulty was said to have been experienced, however, in the rearrangement of 6-nitramino-3-pyridinesulfonic acid^{55, 73} to the 5-nitro derivative, but this observation has recently been contradicted.⁷⁴ Under mild conditions only the nitramino derivative is formed which requires heating to 90° before it undergoes rearrangement. The deactivating influence of a nitro group *para* to the amino function is clear from the fact that vigorous conditions (sulfuric acid at 150°) are required to rearrange 2-nitramino-5-nitropyridine (**25**) to the 3,5-dinitro compound **26**, whereas a 90% yield of **26** is obtained at room temperature from 2-nitramino-3-nitropyridine (**27**).⁵⁴



The rearrangement of 4-nitraminopyridine is unexceptional in proceeding to 4-amino-3-nitropyridine.⁷⁵ Rearrangement of 2-iodo-4-nitraminopyridine gave 4-amino-2-iodo-3 (or 5)-nitropyridine.^{75a} Nitration of 4,4'-dipyridylamine gives the 3,3'-dinitro derivative.⁷⁶ On the other hand, 3-nitraminopyridine and its ring substitution

⁶⁷ R. Adams, J. Hine, and J. Campbell, *J. Am. Chem. Soc.* **71**, 387 (1949).

⁶⁸ T. Takahashi and J. Shibasaki, *J. Pharm. Soc. Japan* **72**, 431 (1952); *Chem. Abstr.* **47**, 6404 (1953).

⁶⁹ A. E. Tschitschibabin and V. S. Tyazhelova, *J. Russ. Phys. Chem. Soc.* **50**, 483 (1918); *Chem. Zentr.* **94** (part III), 1021 (1923); *Chem. Abstr.* **18**, 1495 (1924).

⁷⁰ C. L. Leese and H. N. Rydon, *J. Chem. Soc.* **1954**, 4039.

⁷¹ O. Yu. Magidson and G. P. Menshikoff, *Trans. Sci. Chem.-Pharm. Inst. (Moscow)* No. 16, 23 (1926); *Chem. Abstr.* **23**, 1640 (1929).

⁷² C. R  th and G. Prange, *Ann.* **467**, 1 (1928).

⁷³ C. R  th, *Ann.* **487**, 105 (1931).

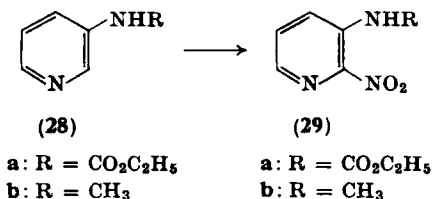
⁷⁴ W. Czuba, *Roczniki Chem.* **34**, 1149 (1960); *Chem. Abstr.* **55**, 14448 (1961).

⁷⁵ E. Koenigs, M. Miedls, and H. Gurlt, *Ber.* **57**, 1179 (1924).

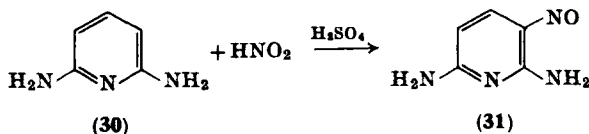
^{75a} K. Lewicku and E. Plazek, *Roczniki Chem.* **39**, 643 (1965).

⁷⁶ E. Koenigs and G. Jung, *J. Prakt. Chem.* **137**, 144 (1953).

products do not rearrange to 3-aminonitropyridine derivatives. Instead, azo-compounds and phenols are formed.^{77, 78} Ethyl 3-pyridylcarbamate (**28a**) does undergo nitration, however, to give a 61% yield of the 2-nitro derivative (**29a**).⁶⁴ Similarly, the *N*-nitro derivative of 3-methylaminopyridine (**28b**) rearranges to (**29b**).⁷⁹ This orientation *ortho* to the amino group will be discussed later.



Two amino groups activate the pyridine nucleus sufficiently that nitrosation can take place: 2,6-diaminopyridine (**30**) reacts with nitrous acid in sulfuric or acetic acid to give the 3-nitroso derivative (**31**),^{80, 81} no deamination taking place.



Halogenation of the aminopyridines takes place very readily, in contrast with that of pyridine itself. A 2-amino group directs the entering halogen to the 5-position and not to the 3-position, attack at C-3 usually only taking place after the first halogen atom has already substituted the C-5 proton, thus resulting in the formation of a 3,5-disubstituted derivative. Chlorination of 2-aminopyridine in cold ethanol gave 2-amino-5-chloropyridine (68%) which, under more vigorous conditions, gave 2-amino-3,5-dichloropyridine.⁸² Good yields were also obtained using HCl and H₂O₂ at 85°. ^{82a} No 2-amino-

⁷⁷ W. Czuba, *Roczniki Chem.* **34**, 905, 1639, and 1647 (1960).

⁷⁸ W. Czuba, *Bull. Acad. Polon. Sci., Ser. Sci. Chim.* **8**, 281 (1960).

⁷⁹ E. Plazek, A. Marcinikow, and C. Stammer, *Roczniki Chem.* **15**, 365 (1935); *Chem. Abstr.* **30**, 1377 (1936).

⁸⁰ J. M. Cox, J. A. Elvidge, and D. E. H. Jones, *J. Chem. Soc.* **1964**, 1423.

⁸¹ H. Graboyes and A. R. Day, *J. Am. Chem. Soc.* **79**, 6421 (1957).

⁸² A. E. Tschitschibabin and A. F. Egorov, *J. Russ. Phys. Chem. Soc.* **60**, 683 (1938); *Chem. Abstr.* **23**, 2182 (1929).

^{82a} F. Friedrich and R. P. Fabini, *Pharmazie* **19**, 677 (1964).

3-chloropyridine was reportedly formed. Here again, the activating and predominantly *para*-directing influence of the 2-amino group is obvious. Bromination of 2-aminopyridine in ethanol or sulfuric acid solution proceeds similarly, to give first 2-amino-5-bromopyridine and then 2-amino-3,5-dibromopyridine.^{69, 70, 83-85} 2-Acetamidopyridine similarly gives the 5-bromo derivative,⁶³ the acetamido group being, as usual, less activating than the free amino group. Thus, a quantitative yield of 2-acetamido-5-bromo-4,6-dimethylpyridine is obtained from 2-acetamido-4,6-lutidine with *N*-bromosuccinimide (the free amine gives the dibromo compound under these conditions).⁸⁶ Alkylsulfonyl derivatives of 2-aminopyridine undergo chlorination and bromination in dichloroethane solution at room temperature, substitution occurring at C-5.⁸⁷ The 2-dimethylamino group is similarly predominantly *para*-directing in bromination.⁶⁰ The 2-amino group is sufficiently activating to overcome the influence of a nitro or a sulfonic acid substituent: 2-amino-3-nitropyridine reacts with bromine and sulfuric acid to give 2-amino-5-bromo-3-nitropyridine; the 5-nitro compound gives the corresponding 3-bromo derivative⁸⁸; and bromination of 2-amino-5-pyridine sulfonic acid in aqueous solutions gives the 3-bromo derivative.⁷³ The products obtained in the bromination of other derivatives of 2-aminopyridine and the conditions used are summarized in Table II.

Iodination of 2-aminopyridine under a variety of experimental conditions gives, in all cases, 2-amino-5-iodopyridine when only one molar equivalent of iodine is used. Yields range as high as 90%.^{67, 71, 89-94} The *N*-monoalkyl and *N,N*-dialkyl derivatives behave similarly.⁹²

There are no reports of studies on the chlorination or bromination

⁸³ H. L. Bradlow and C. A. Vander Werf, *J. Org. Chem.* **16**, 73 (1951).

⁸⁴ F. H. Case, *J. Am. Chem. Soc.* **68**, 2574 (1946).

⁸⁵ H. J. den Hertog and P. Bruin, *Rec. Trav. Chim.* **65**, 385 (1946).

⁸⁶ R. P. Mariella and E. P. Belcher, *J. Am. Chem. Soc.* **74**, 1916 (1952).

⁸⁷ A. G. Kostsova, *J. Gen. Chem. USSR* **33**, 588 (1963).

⁸⁸ A. E. Tschitschibabin, *J. Russ. Phys. Chem. Soc.* **50**, 492 (1918); *Chem. Abstr.* **18**, 1495 (1924).

⁸⁹ W. T. Caldwell, F. T. Tyson, and L. Lauer, *J. Am. Chem. Soc.* **66**, 1479 (1944).

⁹⁰ K. Vieweg, German Patent 526,803; *Chem. Abstr.* **25**, 4807 (1931).

⁹¹ G. Kochendoerfer, German Patent 513,293; *Chem. Abstr.* **25**, 1263 (1931).

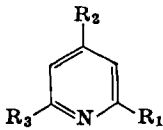
⁹² Schering-Kahlbaum A.G., German Patent 503,920; *Chem. Abstr.* **24**, 5769 (1930).

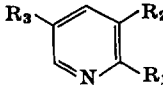
⁹³ J. P. Wibaut and H. J. den Hertog, German Patent 574,655; *Chem. Abstr.* **27**, 4542 (1933).

⁹⁴ O. Yu. Magidson and G. P. Menschikoff, *Ber.* **58**, 113 (1925).

TABLE II

BROMINATION OF SOME SUBSTITUTED 2-AMINOPYRIDINE DERIVATIVES

|  | | | | | |
|---|-------------------------------|-----------------|---|--|------------------------|
| R ₁ | R ₂ | R ₃ | Conditions | Products | Reference ^a |
| NH ₂ | CH ₃ | H | Br ₂ | 5-Bromo | 81 |
| NH ₂ | H | CH ₃ | Br ₂ | 5-Bromo | 81 |
| NH ₂ | H | CH ₃ | Br ₂ , 20% H ₂ SO ₄ , 0° | 5-Bromo | 95 |
| | | | Br ₂ , 20% H ₂ SO ₄ , < 35° | 3,5-Dibromo | 95 |
| NH ₂ | CH ₃ | CH ₃ | Br ₂ | 5-Bromo | 81 |
| NH ₂ | Br | H | Br ₂ , AcOH, 0° | 5-Bromo | 96 |
| | | | Br ₂ , AcOH, room temp. | 3,5-Dibromo | 96 |
| NH ₂ | H | Br | Br ₂ , AcOH, 0° | 5-Bromo (50%) and 3,5-dibromo (15%) | 96 |
| NH ₂ | Br | Br | Br ₂ , AcOH, 0° | 5-Bromo and 3,5-dibromo | 96 |
| NH ₂ | C ₂ H ₅ | H | Br ₂ , H ₂ SO ₄ , 100°, 4 hours | 3,5-Dibromo (65%) | 97 |

|  | | | | | |
|--|-----------------|-----------------|--|----------|-----------|
| R ₁ | R ₂ | R ₃ | Conditions | Products | Reference |
| NHCH ₃ | NO ₂ | H | Br ₂ , H ₂ SO ₄ | 5-Bromo | 98 |
| NHCH ₃ | H | NO ₂ | Br ₂ , H ₂ SO ₄ | 3-Bromo | 98 |
| NH ₂ | Br | H | Br ₂ , AcOH, room temp. | 5-Bromo | 51 |

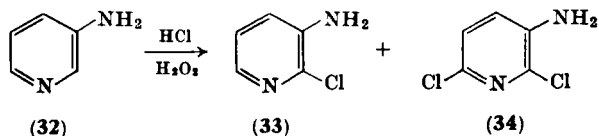
^a See footnotes.

of 4-aminopyridine itself, but there is no reason to doubt that substitution at C-3 and C-5 would occur readily. Iodination with iodine monochloride in hydrochloric acid solution gives a mixture of the 3-iodo and

⁹⁵ R. Adams and A. W. Schrecker, *J. Am. Chem. Soc.* **71**, 1186 (1949).⁹⁶ H. J. den Hertog, *Rec. Trav. Chim.* **65**, 129 (1946).⁹⁷ K. Halvarson, *Arkiv Kemi* **7**, 225 (1954); *Chem. Abstr.* **50**, 335 (1956).⁹⁸ A. E. Tschitschibabin and A. V. Kirssanow, *Ber.* **61**, 1223 (1928).

3,5-diiodo derivatives.^{99, 100} Bromination of substituted 4-aminopyridines takes place normally.^{98, 101} For example, 4-amino-3-nitropyridine reacts with bromine in acetic acid to give 4-amino-5-bromo-3-nitropyridine.⁷⁵

Whereas the 2-amino group is predominantly *para*-directing in the above electrophilic substitutions, a 3-amino group directs the entering halogen to C-2 (as was the case with the nitration of 3-methylaminopyridine). Thus, chlorination of 3-aminopyridine (**32**) at 80° with hydrochloric acid and hydrogen peroxide gave 3-amino-2-chloropyridine (**33**) (88%) together with a small amount of 3-amino-2,6-dichloropyridine (**34**).¹⁰² Under these conditions, the pyridinium salt is probably the species undergoing substitution. Under more vigorous conditions (110°) the yield of **34** is increased to 5.7%, and some fully



substituted aminotetrachloropyridine is also obtained unexpectedly. Chlorination of 3-methylaminopyridine under the conditions¹⁰² described for 3-aminopyridine is said not to yield the expected 2-chloro-3-methylaminopyridine.^{102a} Bromination of 3-aminopyridine takes place even more readily, for the 2,6-dibromo compound is the one isolated, together with some 2,4,6-tribromo compound.^{102, 103} 3-Dimethylaminopyridine gave a mixture of the 2-bromo and 2,6-dibromo derivatives, but 3-methylaminopyridine only gave the 2,6-dibromo compound.⁷⁹ The amino group is mainly *para*-directing in electrophilic aromatic substitutions in the benzene series, and the acetamido group also gives rise to *o*:*p*-ratios of less than one. This tendency is also evident in the reactions of the 2-aminopyridines. With the 3-aminopyridines, however, the situation is much more reminiscent of that in the benzene series when an *ortho-para*-orienting

⁹⁹ J. Reitmann, German Patent 579,224; *Chem. Abstr.* **27**, 4880 (1933).

¹⁰⁰ I. G. Farbenindustrie A.-G., French Patent 728,634; *Chem. Abstr.* **26**, 6071 (1932).

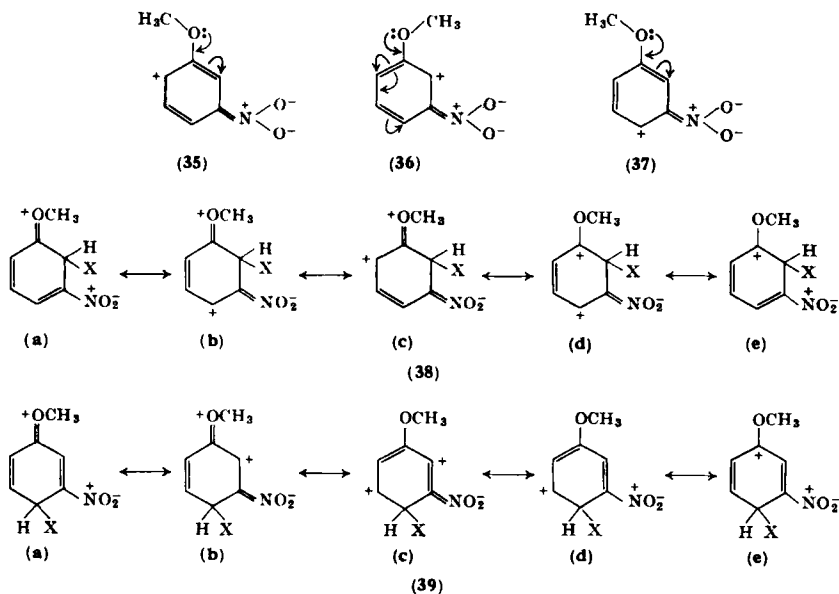
¹⁰¹ W. Marckwald, *Ber.* **27**, 1317 (1894).

¹⁰² O. von Schiekh, A. Binz, and A. Schulz, *Ber.* **69**, 2593 (1936).

^{102a} J. W. Clark-Lewis and M. J. Thompson, *J. Chem. Soc.* **1957**, 442.

¹⁰³ E. Plazek and A. Marcinkow, *Roczniki Chem.* **14**, 326 (1934); *Chem. Abstr.* **29**, 2535 (1935).

substituent is *meta* to a strongly *meta*-orienting one: in this case, electrophilic substitution often occurs between them, contrary to the principle of the additivity of the effects of substituents. Examples are *m*-hydroxybenzaldehyde,¹⁰⁴ *m*-nitrophenol,¹⁰⁵ and *m*-nitroanisole.¹⁰⁶ It has been suggested¹⁰⁷ that the mesomeric effect of the electron-withdrawing group favors the *para*-quinonoid contributing structure such as **35** more than it does **36** so that **35** has a higher coefficient in the ground state wave function than does **36**. Electromeric electron-release from the methoxyl group will then occur preferentially as indicated in **35**. Contributions from **37** and the corresponding electromeric shifts would, again, favor attack at C-2. An explanation based on a consideration of the number of canonical structures contributing to the intermediate σ -complex has also been put forward.¹⁰⁸ Neglecting structures with like charges on adjacent



¹⁰⁴ H. H. Hodgson and H. G. Beard, *J. Chem. Soc.* **1925**, 876; **1926**, 148.

¹⁰⁵ F. W. Schlieper, *Ber.* **26**, 2466 (1893).

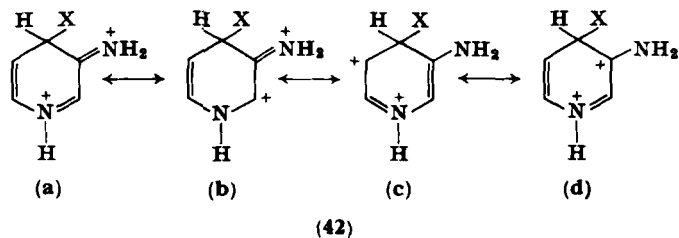
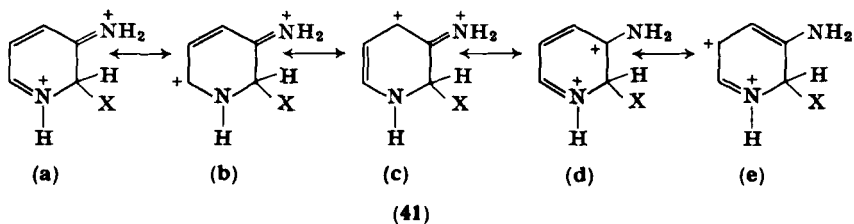
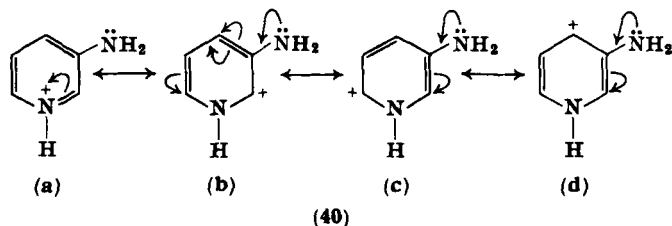
¹⁰⁶ A. F. Holleman, *Rec. Trav. Chim.* **22**, 263 (1903).

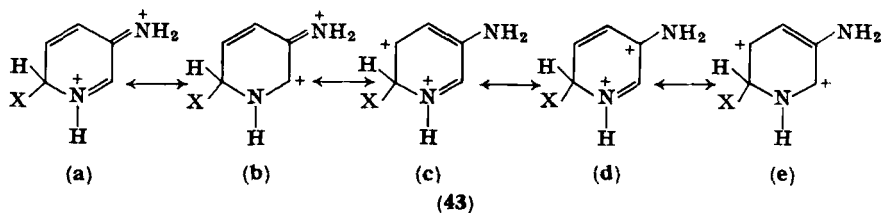
¹⁰⁷ C. K. Ingold, "Structure and Mechanism in Organic Chemistry," p. 268. G. Bell, London, 1953.

¹⁰⁸ J. Hine, "Physical Organic Chemistry," 2nd ed., p. 380. McGraw-Hill, New York, 1962.

atoms, one can write five contributing structures, for each, of attack at C-2 (38a-e) and C-4 (39a-e). However, attack at C-2 leads to a greater participation of the lone-pair of electrons on the methoxyl group than does attack at C-4. In the benzene series attack at C-2 is seldom exclusive and by no means always dominant, steric factors entering into play with increasing size of the attacking reagent.

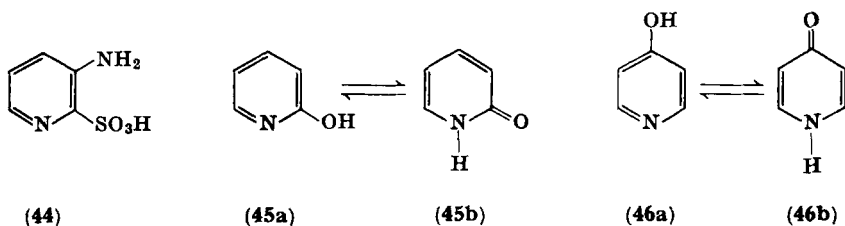
Similar explanations may be put forward to account for the results in the pyridine series. While there is no obvious reason why a structure such as 40c should contribute more to the resonance hybrid than 40b, 40d might be expected to be most stable of these three, leading to the observed predominant orientation. The intermediate σ -complex explanation must again consider greater participation of the unshared valence electrons on the amino group in the delocalization of the positive charge in the case of attack at C-2 (41a-e) than at C-4 (42a-d) or C-6 (43a-e). In this case there should be no, or almost no, steric effect hindering the approach of the reagent. It is interesting to note,





therefore, that in a case where the steric effect might conceivably come into operation—that of the bromination of 3-hydroxypyridine *N*-oxide—the only product of monosubstitution still involves attack at C-2.⁶² (Steric hindrance does become apparent, however, in the iodination of 3-hydroxypyridine *N*-oxide when position 2 remains unsubstituted.⁶²) Another possible explanation for the observed orientation, involving the postulation of lower entropies of activation due to hindrance to solvation in substitutions at C-2, will be discussed more fully in the section on nucleophilic substitution reactions which provide some evidence for this sort of phenomenon.

Sulfonation of 2-aminopyridine gives the 5-sulfonic acid exclusively.^{55, 109, 110} 3-Aminopyridine reacts with chlorosulfonic acid to give 3-amino-2-pyridinesulfonic acid (44).^{103, 111} 4-Amino-3-pyridinesulfonic acid is obtained from 4-aminopyridine.¹¹² Arsonation of



2-aminopyridine with As_2O_5 at 200° is reported to give the 5-arsonic acid.¹¹³ Thiocyanation of 2,6-diaminopyridine with "nascent" thiocyanogen (from ammonium thiocyanate, bromine, and 50%

¹⁰⁹ A. E. Tschitschibabin and M. Vialatout, *Bull. Soc. Chim. France* **6**, 736 (1939).

¹¹⁰ C. Naegeli, W. Kündig, and H. Brandenburger, *Helv. Chim. Acta* **21**, 1746 (1938).

¹¹¹ E. Plazek, *Roczniki Chem.* **17**, 97 (1937); *Chem. Abstr.* **31**, 4669 (1937).

¹¹² E. Koenigs and O. Jungfer, *Ber.* **57**, 2080 (1924).

¹¹³ A. Binz and C. Räth, German Patent 537,896 (1924); *Chem. Abstr.* **26**, 1301 (1932).

acetic acid) gives the 3-thiocyanato and 3,5-dithiocyanato derivatives.¹¹⁴ 2,6-Diamino-3-picoline gives the 5-thiocyanato compound. The presence of two activating substituents is necessary to introduce the SCN group into the pyridine nucleus.^{114, 115} Azo-coupling takes place readily at C-6 of 2-alkoxy-3,5-diaminopyridines.^{115a}

4. *Hydroxypyridines and Ethers*

A methoxyl group behaves very similarly to an amino substituent. Nitration of 2-methoxypyridine is reported to give 2-methoxy-5-nitropyridine¹¹⁶; 2-ethoxypyridine gives 2-ethoxy-5-nitropyridine,¹¹⁷ no other isomer being formed; but 3-ethoxypyridine reacts with fuming nitric acid in concentrated sulfuric acid at 60° to yield 75–80% of the 2-nitro compound.¹¹⁸ Again no other isomer was detected. The 3-methyl ether was originally reported to undergo only dinitration¹¹⁹ but has since been found to undergo mononitration at 5° to give 3-methoxy-2-nitropyridine.¹²⁰ Attack at C-4 has not been observed.

The aromatic phenolic group is usually mainly *para*-directing in electrophilic aromatic substitution reactions. Nitrosation and azo-coupling of phenol take place predominantly in the *para*-position,¹²¹ as also does bromination.¹²² On the other hand, nitration of phenol under very mild conditions gives much more of the *ortho*-isomeride (usually in amounts higher than 40% of the total),¹²¹ and chlorination gives rise to an *o*:*p*-ratio of 1.¹²² Such variations in the *o*:*p*-ratio have been attributed to the polarizability of the substituent which can conjugate more or less effectively with the entering electrophile.¹²¹ The amount of electromeric assistance demanded by the reagent from the phenolic group (and hence the geometry of the transition state) will also vary, depending upon its selectivity or reactivity. In the case

¹¹⁴ J. A. Baker and S. A. Hill, *J. Chem. Soc.* **1962**, 3464.

¹¹⁵ A. Maggiolo, *J. Am. Chem. Soc.* **73**, 5815 (1951).

^{115a} J. Barycki and E. Plazek, *Roczniki Chem.* **38**, 553 (1964).

¹¹⁶ A. Haack, German Patent 568,549; *Chem. Abstr.* **27**, 2697 (1933).

¹¹⁷ C. Räth, *Ann.* **484**, 52 (1930).

¹¹⁸ H. J. den Hertog, C. Jouwersma, A. A. van der Wal, and E. C. C. Willebrands-Schogt, *Rec. Trav. Chim.* **68**, 275 (1949).

¹¹⁹ E. Koenigs, H. C. Gardes, and A. Sirot, *Ber.* **61**, 1022 (1928).

¹²⁰ J. Bernstein, B. Stearns, E. Shaw, and W. A. Lott, *J. Am. Chem. Soc.* **69**, 1151 (1947).

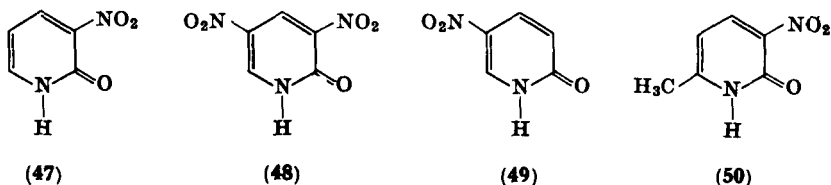
¹²¹ C. K. Ingold, "Structure and Mechanism in Organic Chemistry," p. 265. G. Bell, London, 1953.

¹²² P. B. D. de La Mare and J. H. Ridd, "Aromatic Substitution: Nitration and Halogenation," p. 131. Butterworth, London and Washington, D.C., 1959.

of the 2- and 4-hydroxypyridines, another very important factor has to be taken into account, namely, that these compounds exist mainly in the pyridone forms (**45b**, **46b**) in their ground state and in solution^{122a} and could react in either tautomeric modification depending upon the conditions of the reaction.

Deuteration of *N*-methyl-4-pyridone occurs at C-2 and C-6 in alkaline (but not acidic or neutral) solution.^{122b}

Nitration of 2-pyridone, originally thought to give mainly 3-nitro-2-pyridone (**47**) together with some 3,5-dinitro-2-pyridone (**48**) and a trace of the 5-nitro derivative (**49**),¹²³ was later shown to give a mixture of **47** and **48**.¹²⁴ Similarly, reaction of 6-methyl-2-pyridone with nitric acid in glacial acetic acid gave the product of nitration at C-3 (**50**).¹²⁵ This preferential *ortho*-nitration is in marked contrast to



the behavior of the 2-methyl ether and suggests that it is the molecule in the pyridone form (**45b**) which is undergoing substitution. Chelation in the transition complex between the entering nitro group and the hydroxyl group has also been suggested as an explanation for the observed orientation.¹²⁶ The presence of deactivating nitro or carboxyl groups does not impede the reaction appreciably: both 3- and 5-nitro-2-pyridone give (**48**).^{124, 127} 6-Hydroxynicotinic acid gives 6-hydroxy-5-nitronicotinic acid on treatment with fuming nitric acid at 50°. Under more vigorous conditions, decarboxylation and dinitration to **48** occur.¹²⁴ *N*-Methyl-2-pyridone (**51**) also undergoes nitration¹²⁸ with 62% nitric acid in the absence of sulfuric acid to give

^{122a} A. R. Katritzky and J. M. Lagowski, "Advances in Heterocyclic Chemistry" (A. R. Katritzky, ed.), Vol. 1, p. 339. Academic Press, New York, 1963.

^{122b} P. Beak and J. Bonham, *Tetrahedron Letters* **1964**, 3083.

¹²³ A. Binz and H. Maier-Bode, *Angew. Chem.* **49**, 486 (1936).

¹²⁴ A. H. Berrie, G. T. Newbold, and F. S. Spring, *J. Chem. Soc.* **1951**, 2590.

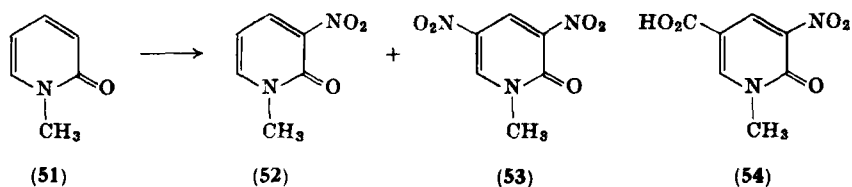
¹²⁵ C. A. Salemink and G. M. van der Want, *Rec. Trav. Chim.* **68**, 1013 (1949).

¹²⁶ K. Schofield, *Quart. Rev.* **4**, 382 (1950).

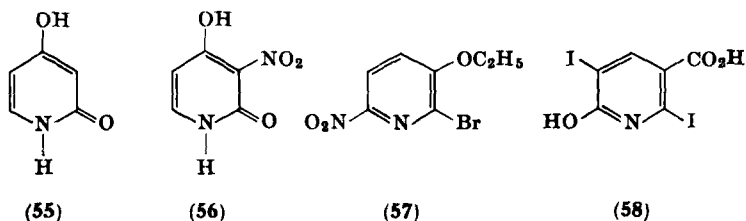
¹²⁷ J. Kozłowska and E. Plazek, *Roczniki Chem.* **33**, 831 (1959); *Chem. Abstr.* **54**, 3410 (1960).

¹²⁸ O. Fischer and M. Chur, *J. Prakt. Chem.* **93**, 363 (1916).

a mixture of the 3-nitro (52) and the 3,5-dinitro (53) compounds.^{124, 129, 130} The predominant *ortho*-orientation again supports the suggestion that nitration of the 2-pyridone tautomer is occurring in those cases where the ring nitrogen is unsubstituted. *N*-Methyl-2-pyridone-5-carboxylic acid reacts with fuming nitric acid at 55° to give *N*-methyl-3-nitro-2-pyridone-5-carboxylic acid (54).¹²⁴



4-Pyridone undergoes mono- and dinitration at the β -positions very readily.¹³¹⁻¹³³ Nitration of 2,4-dihydroxypyridine (which probably exists in the 2-pyridone form, 55) occurs under very mild conditions and yields the 3-nitro product 56.^{134, 135} If C-3 is blocked by a carbethoxyl group, nitration at C-5 takes place very readily.^{136, 137} Unlike the monohydroxypyridines, which do not react with nitrous acid, 2,6-dihydroxypyridine (presumably mainly 6-hydroxypyrid-2-one) undergoes nitrosation at C-3.¹³⁸



¹²⁹ A. E. Tschitschibabin and R. A. Konowalowa, *Ber.* **58**, 1712 (1925).

¹³⁰ A. E. Tschitschibabin and R. A. Konowalowa, *Ber.* **59**, 2055 (1926).

¹³¹ E. Koenigs and K. Freter, *Ber.* **57**, 1189 (1924).

¹³² E. Koenigs and A. Fulde, *Ber.* **60**, 2107 (1927).

¹³³ W. H. Crowe, *J. Chem. Soc.* **1925**, 2028.

¹³⁴ F. Kögl, G. M. van der Want, and C. A. Salemink, *Rec. Trav. Chim.* **67**, 29 (1948).

¹³⁵ H. J. den Hertog, J. C. M. Schogt, J. de Bruyn, and A. de Klerk, *Rec. Trav. Chim.* **69**, 673 (1950).

¹³⁶ J. Klosa, *Arch. Pharm.* **285**, 453 (1952).

¹³⁷ W. F. Bruce and L. A. Perez-Medina, *J. Am. Chem. Soc.* **69**, 2571 (1947).

¹³⁸ L. Gattermann and A. Skita, *Ber.* **49**, 494 (1916).

As in the case of the corresponding amine, nitration of 3-hydroxypyridine occurs mainly at C-2 rather than at the other *ortho*- or at the *para*-position.¹³⁹ 3-Ethoxypyridine similarly gives the 2,3-disubstituted derivative in 75–80% yield with fuming nitric acid in sulfuric acid.^{118, 119} Only a trace of the 6-nitro derivative is apparently formed, as indicated by paper chromatography of the corresponding amines.¹⁴⁰ Under mild conditions (5°) 3-methoxypyridine also gives the 2-mononitro derivative¹²⁰ which, under more vigorous conditions, gives 2,6-dinitro-3-methoxypyridine.¹¹⁹ Nitration at C-4 is never observed, even when C-2 is blocked as in 2-bromo-3-ethoxypyridine: in this case only 2-bromo-3-ethoxy-6-nitropyridine (57) is formed.¹⁴¹

Halogenation of the hydroxypyridines takes place with ease and is difficult to control in many instances. In most cases, the reaction with 2-pyridone gives rise to the 3,5-dihalogeno-2-pyridone, even under mild conditions. This applies to the bromination with bromine water^{142, 143} and iodination with iodine monochloride in acid¹⁴⁴ or iodine in potassium carbonate solution.⁸⁹ Only three cases of monohalogenation have been reported: (i) the formation of 5-chloro-2-pyridone, together with 3,5-dichloro-2-pyridone, by the action of chlorine in chloroform¹⁴⁴; (ii) the chromatographic detection of 3- and 5-bromo-2-pyridone, together with 3,5-dibromo-2-pyridone, on bromination in piperidine¹⁴⁵; and (iii) the isolation of 5-iodo-2-pyridone (33.5%) together with 3,5-diiodo-2-pyridone (26.5%) when iodine-potassium iodide in aqueous sodium carbonate solution is used.¹⁴⁶ In these cases, the 2-hydroxyl group appears to be predominantly *para*-directing, in contrast to the situation observed in nitration, and might lend some support to the concept¹²⁶ of a cyclic intermediate in the transition state in the latter case, or might just be a result of a greater electron demand in the transition state by the less active reagent in the case of halogenation. Deactivating substituents again appear to have little effect upon the ease of substitution. Thus, 5-nitro-2-

¹³⁹ E. Plazek and Z. Rodewald, *Roczniki Chem.* **16**, 502 (1936).

¹⁴⁰ H. G. Bray, F. C. Neale, and W. V. Thorpe, *Biochem. J.* **46**, 506 (1950).

¹⁴¹ H. J. den Hertog, C. Jouwersma, A. A. van der Wal, and E. C. C. Willebrands-Schogt, *Rec. Trav. Chim.* **68**, 4 (1949).

¹⁴² W. Königs and R. Geigy, *Chem. Ber.* **17**, 1832 (1884).

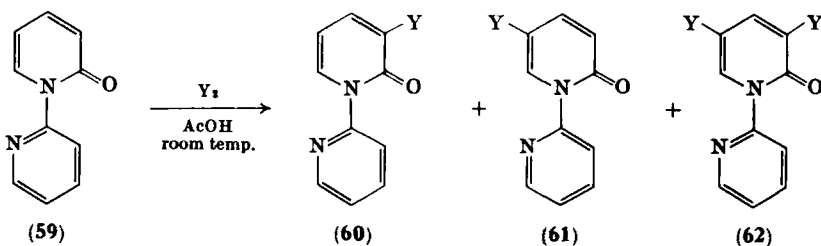
¹⁴³ M. van Ammers and H. J. den Hertog, *Rec. Trav. Chim.* **75**, 1259 (1956).

¹⁴⁴ M. Dohrn and R. Dirksen, U.S. Patent 1,706,775; *Chem. Abstr.* **23**, 2189 (1929).

¹⁴⁵ F. Ramirez, Unpublished results quoted by H. Meislich.¹⁵²

¹⁴⁶ F. W. Broekman and H. J. C. Tendeloo, *Rec. Trav. Chim.* **81**, 107 (1962).

pyridone gives the 3-chloro¹⁴⁷ and 3-iodo derivatives⁹¹ readily. 6-Hydroxypicolinic acid and its 4-chloro derivative undergo 3,5-dihalogenation in alkaline solution (in which medium the compound is present as the mono- or di-anion).¹⁴⁸ The reported formation of 2,5-diiodo-6-hydroxynicotinic acid (**58**) by the action of iodine and potassium iodide in aqueous ammonia on 6-hydroxynicotinic acid is surprising because it represents attack *meta* to the hydroxyl group,¹⁴⁹ and confirmation of the proposed structure seems to be desirable. *N*-Substituted 2-pyridones also undergo electrophilic substitution readily. Thus, *N*-(2'-pyridyl)-2-pyridone (**59**) has been reported to react with one mole of bromine to give an excellent yield of the 3-bromo compound (**60**, Y = Br).¹⁵⁰ Repetition of this bromination in acetic acid followed by gas chromatographic analysis of the reaction product indicated that **60** (Y = Br) was indeed the major product formed (50–55%), but that a 15–20% yield of *N*-(2'-pyridyl)-5-bromo-2-pyridone (**61**, Y = Br) was also present, as well as a small amount of the 3,5-dibromo derivative (**62**, Y = Br) (3%).¹⁵¹ This *o*:*p*-ratio of 3–4:1 is to be contrasted with that obtained in the chlorination of **59** with chlorine in acetic acid at room temperature, i.e., **60** (Y = Cl)/**61**



(Y = Cl) = 0.5.¹⁵¹ In the latter case, the remainder of the reaction mixture (25%) consisted of equal parts of **62** (Y = Cl) and starting material. This interesting difference in orientation in chlorination and bromination under otherwise essentially identical conditions may reflect a difference in the polarization, and hence the selectivity, of the

¹⁴⁷ T. Takahashi and J. Shibasaki, *J. Pharm. Soc. Japan* **72**, 378 (1952); *Chem. Abstr.* **47**, 6403 (1953).

¹⁴⁸ R. Graf, *J. Prakt. Chem.* **148**, 13 (1937).

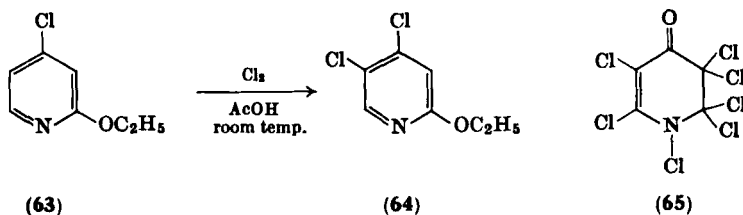
¹⁴⁹ A. Burger and M. S. Bailey, *J. Am. Chem. Soc.* **68**, 520 (1946).

¹⁵⁰ F. Ramirez and P. W. von Ostwalden, *Chem. Ind. (London)* **1957**, 46; *J. Am. Chem. Soc.* **81**, 156 (1959).

¹⁵¹ H. J. den Hertog, D. J. Buurman, and P. A. de Villiers, *Rec. Trav. Chim.* **80**, 325 (1961).

attacking reagent in the reaction medium. Any steric effect might have been expected to act in the opposite sense to that observed. In most cases, *N*-substituted 2-pyridones undergo 3,5-dihalogenation, e.g., with chlorine in acetic acid *N*-methyl-2-pyridone gives the 3,5-dichloro compound.¹²⁸ Other examples of this type of reaction have been summarized.¹⁵² The reaction of cyanogen bromide with *N*-methyl-5-nitro-2-pyridone resulted in the formation of the 3-bromo derivative.¹¹⁷ *N*-Bromosuccinimide has been used to effect the bromination of some 2-pyridones and their *N*-methyl derivatives.¹⁵³

Ethers are halogenated normally. Thus, monochlorination of 4-chloro-2-ethoxypyridine (**63**) occurs in the 5-position to give **64**,¹⁵⁴ no 3-chloro compound being detected.



4-Pyridones behave as expected and are usually dihalogenated at the 3- and 5-positions, e.g., the iodination of 2,6-dimethyl-4-pyridone¹⁵⁵ and of 4-pyridone,⁹⁹ and the chlorination and iodination of 4-pyridone-2-carboxylic acid.¹⁵⁶ On the other hand, the exhaustive chlorination of 4-pyridone with sulfuryl chloride gives the heptachloro-1,2,3,4-tetrahydro-4-pyridone (**65**).¹⁵⁷

The halogenation of 2,4-dihydroxypyridine and of the ethers derived therefrom has led to some interesting observations.¹⁵⁸ Bromination of 2,4-dihydroxypyridine (presumably in the 2-pyridone form, **55**) gives the 3-bromo derivative, no attack taking place at the

¹⁵² H. Meislich, in "Pyridine and Its Derivatives" (E. Klingsberg, ed.), Pt. III, Chapter 12, p. 509. Wiley (Interscience), New York, 1962.

¹⁵³ D. J. Cook, R. E. Bowen, P. Sorter, and E. Daniels, *J. Org. Chem.* **26**, 4949 (1961).

¹⁵⁴ C. R. Kolder and H. J. den Hertog, *Rec. Trav. Chim.* **72**, 285 (1953).

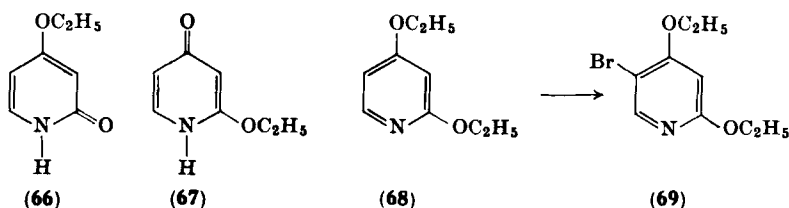
¹⁵⁵ E. Ochiai and M. Fujimoto, *Pharm. Bull. (Tokyo)* **2**, 131 (1954); *Chem. Abstr.* **50**, 990 (1956).

¹⁵⁶ M. Dohrn and P. Diedrich, *Ann.* **494**, 284 (1932).

¹⁵⁷ H. J. den Hertog, J. Maas, C. R. Kolder, and W. P. Combé, *Rec. Trav. Chim.* **74**, 59 (1955).

¹⁵⁸ C. R. Kolder and H. J. den Hertog, *Rec. Trav. Chim.* **79**, 474 (1960).

5-position. The same applies to the bromination of 4-ethoxy-2-pyridone (66) and of 2-ethoxy-4-pyridone (67), the carbon atom between the C=O and C—OR groups being the most reactive one in the molecule. On the other hand, as with resorcinol, 2,4-diethoxypyridine (68) is substituted at C-5 to give 69. It has been suggested that the orientation of the reagent to that position is enhanced because the 3-position is sterically hindered by the ethoxyl groups.



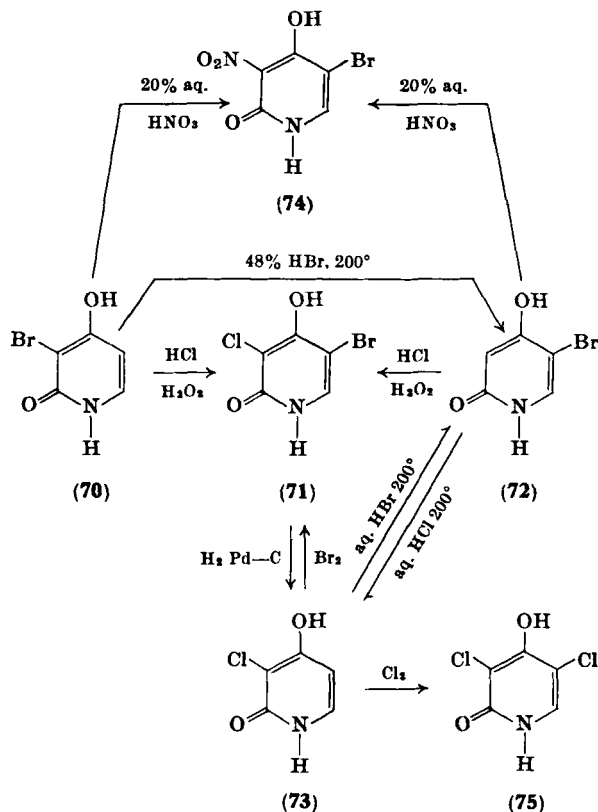
This may only be a partial explanation. The halogenated 2,4-dihydropyridines undergo some rather unusual molecular rearrangements,^{154, 159-161} the mechanisms of which are still not clear. These reactions have already been discussed¹⁵² and are only summarized here briefly. Chlorination of 3-bromo-2,4-dihydropyridine (70) with hydrochloric acid and hydrogen peroxide gives 5-bromo-3-chloro-2,4-dihydropyridine (71) which is also obtained from 5-bromo-2,4-dihydropyridine (72) and from the bromination of 3-chloro-2,4-dihydropyridine (73).¹⁵⁹ Similarly, nitration of 70 with hot aqueous nitric acid gave the 3-nitro-5-bromo compound 74 which was also obtained by the nitration of 72, albeit in much higher yield. Chlorination of 73 gives the 3,5-dichloro derivative 75 in good yield.¹⁶⁰ This speaks against a mechanism the first step of which is the formation of 2,4-dihydropyridine and halogen, followed by rehalogenation: had this been the case, then some 75 might have been expected to be formed in the chlorination of 70, whereas none was detected (nor was any 3,5-dibromo derivative found). On the other hand, it is hard to picture an intramolecular process for this halogen migration from C-3 to C-5 unless some sort of a bridged (perhaps bimolecular?) transition state is involved. In contrast to 72 and 73 the halogen in 5-chloro-2,4-dihydropyridine is quite stable and is not

¹⁵⁹ H. J. den Hertog and J. C. M. Schogt, *Rec. Trav. Chim.* **70**, 353 (1951).

¹⁶⁰ C. R. Kolder and H. J. den Hertog, *Rec. Trav. Chim.* **72**, 853 (1953).

¹⁶¹ H. J. den Hertog, W. P. Combé, and C. R. Kolder, *Rec. Trav. Chim.* **73**, 1 (1954).

replaced when it is heated with 48% hydrogen bromide at 250° nor does it migrate when the compound is heated with concentrated hydrochloric acid. Bromination of 5-chloro-2,4-dihydroxypyridine gives the 3-bromo compound without rearrangement.¹⁵⁴ No conclusions could be reached concerning the inter- or intra-molecularity of the rearrangement accompanying nitration of **70**. No dinitro or



dibromo compounds were isolated. On the other hand, the yield of **74** from **70** was much lower (35%) than that from **72** (75%).¹⁶⁰ Bromination of 2,4-dihydroxy-3-nitropyridine gives **74**. When a current of nitrogen was passed through the nitration mixture a *small* amount of bromine was carried over and the yield of **74** was decreased, suggesting the possibility of an intermolecular process.¹⁶⁰ Clearly, more work is desirable on the mechanism of these rearrangements.

Halogenation of the 3-hydroxypyridines follows the pattern set by the 3-aminopyridines in that substitution takes place at the 2-position. Chlorination with hydrochloric acid and hydrogen peroxide,¹⁰² bromination with one equivalent of bromine in pyridine,¹⁶² and iodination with iodine and sodium carbonate¹⁰² all give the 2-halo-3-hydroxypyridine. Chelation and formation of a cyclic transition state does not appear a likely possibility in these reactions. Under more vigorous conditions or with an excess of the halogen, 2,6-disubstitution^{162, 163} and 2,4,6-trisubstitution can occur.¹⁶²

Hydroxypyridines undergo a variety of other electrophilic substitution reactions. Sulfonation of 2-pyridone with 10% oleum at 180° gave the 5-sulfonic acid.^{69, 110} *N*-Methyl-2-pyridone is similarly sulfonated with chlorosulfonic acid. The action of fuming sulfuric acid gave a mixture of the 5-sulfonic acid and the 3,5-disulfonic acid. A nitro group at C-5 is said not to hinder the reaction, sulfonation at the 3-position taking place.¹⁶⁴ 4-Pyridone-3-sulfonic acid is formed from 4-pyridone.¹¹²

Chloromercuration of 2-pyridone at the position *para* to the carbonyl function has been effected using mercuric acetate in acetic acid, followed by treatment with hydrochloric acid.¹⁶⁵ With aqueous mercuric acetate the 3,5-dimercuriacetate was obtained.¹⁶⁶ When 4-pyridone was heated with mercuric acetate on the water-bath and the mixture then treated with sodium chloride, the 3-chloromercury derivative was formed. 3-Hydroxypyridine has to be boiled under reflux with mercuric acetate to effect substitution at C-2.¹⁶⁶

Arsonation of 2-pyridone is effected by fusing it with arsenic acid: the main product is the 5-arsonic acid which is formed together with some 3-arsonic acid.^{165, 167} The reaction appears to be reversible: short reaction times result in the products of kinetic control in which the 5-isomer predominates, whereas heating periods of 24 hours favor the products of thermodynamic control in which the 3-isomer is the

¹⁶² H. J. den Hertog, F. R. Schepman, J. de Bruyn, and G. J. E. Thyse, *Rec. Trav. Chim.* **68**, 1281 (1950).

¹⁶³ H. Bojarska-Dahlig, *Roczniki Chem.* **30**, 475 (1956); *Chem. Abstr.* **51**, 14722 (1957).

¹⁶⁴ O. von Schickh, German Patent 601,896; *Chem. Abstr.* **28**, 7267 (1934).

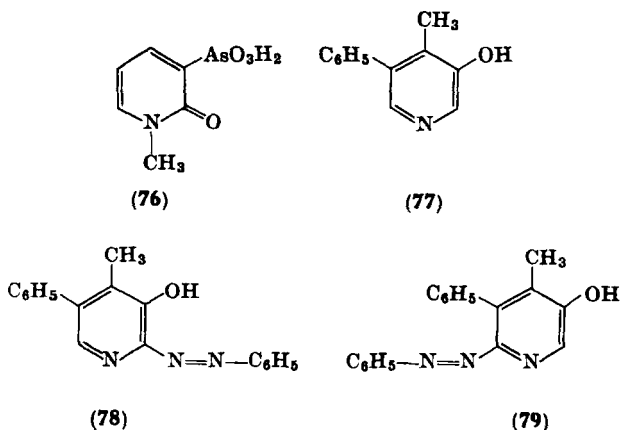
¹⁶⁵ A. Binz, C. R  th, and H. Maier-Bode, *Ann. Chem.* **478**, 22 (1930).

¹⁶⁶ T. Takahashi and F. Yoneda, *Chem. Pharm. Bull. (Tokyo)* **6**, 611 (1958); *Chem. Abstr.* **54**, 14246 (1960).

¹⁶⁷ A. Binz and H. Maier-Bode, *Ann.* **487**, 119 (1931).

main one formed. *N*-Methyl-2-pyridone gives the 3-arsonic acid **76**.¹⁶⁷ Arsonation at C-5 can be effected using different conditions.¹⁶⁸

Azocoupling with 2-pyridone takes place *para* to the carbonyl group to give 5-phenylazo-2-pyridone.¹⁶⁹ The product obtained from 3-hydroxypyridine and benzenediazonium chloride in weak acid has recently been shown to consist of a mixture of 3-hydroxy-6-phenylazopyridine (81%) and 3-hydroxy-2-phenylazopyridine (3%),^{170, 171} coupling again taking place mainly *para* to the hydroxyl group. If a phenyl group is present at C-5, as in 3-hydroxy-4-methyl-5-phenylpyridine (**77**), about equal amounts of the 2- (**78**) and 6-phenylazo (**79**)



derivatives are formed.¹⁷⁰ This has been attributed to the effect (presumably steric, though this was not specified) of the phenyl substituent. Interestingly, it is reported that the coupling of 3-hydroxypyridine with *p*-nitrobenzenediazonium chloride in weak acid solution gives 3-hydroxy-2-*p*-nitrophenylazopyridine exclusively (structure proved by reduction to 2-amino-3-hydroxypyridine).¹⁷² This drastic change in the orientation on going to a more electrophilic

¹⁶⁸ A. Binz and C. R  th, German Patent 525,090; *Chem. Abstr.* **25**, 4012 (1927).

¹⁶⁹ W. H. Mills and S. T. Widdows, *J. Chem. Soc.* **1908**, 1372.

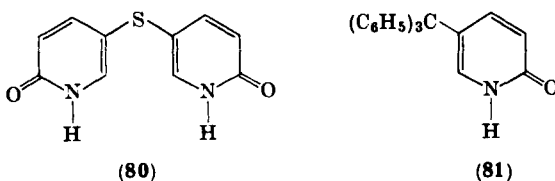
¹⁷⁰ J. A. Moore and F. J. Marascia, *J. Am. Chem. Soc.* **81**, 6049 (1959).

¹⁷¹ R. Urban and O. Schnider, *Helv. Chim. Acta* **47**, 363 (1963).

¹⁷² H. Bojarska-Dahlig and T. Urbański, *Prace Plac  wek Nauk-Badawcz. Min. Przemysłu Chem.* **1952**, 1; *Chem. Abstr.* **48**, 1337 (1954).

diazonium salt needs verification before an attempt is made to assess its meaning. It is worthwhile noting that, under the conditions used in these coupling reactions, no Gomberg-Hey phenylations of the pyridine ring are apparently taking place.

A recent paper describes the reaction of 2-pyridone with sulfur dichloride: when these are boiled in benzene for a week the 5,5'-dipyridyl sulfide (**80**) is formed in 13% yield. The structure of **80** was confirmed by its ultraviolet and nuclear magnetic resonance (NMR) spectra.¹⁷³ 3-Hydroxypyridine gives a poorly defined and apparently high polymeric substance under these conditions, whereas 4-pyridone is said not to react.

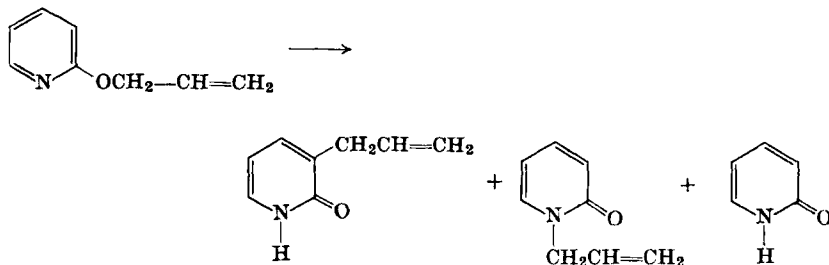


As evidence of the unreactivity of the pyridine nucleus toward electrophilic attack is often cited the fact that it does not undergo Friedel-Crafts acylation or arylation. Two examples of such reactions are, however, known in the 2-hydroxypyridine series. Thus, both 2-pyridone and its *N*-methyl derivative undergo *C*-tritylation with either triphenylmethyl chloride in the absence of a catalyst or with triphenylmethanol in the presence of a small amount of sulfuric acid at 250°. The product obtained with both substrates was assigned the structure of 5-triphenylmethyl-2-pyridone (**81**), though this was not proved.⁶⁷ Although the strong activation of the pyridine nucleus by the hydroxyl function is as expected, it is rather remarkable that it is the relatively stable triphenylmethyl carbonium ion, rather than a more reactive species, that should thus alkylate the nucleus. The aluminum chloride-catalyzed Fries rearrangement of 2-benzoyloxy-pyridine at 180° gives a 1% yield of 5-benzoyl-2-pyridone.⁶⁷

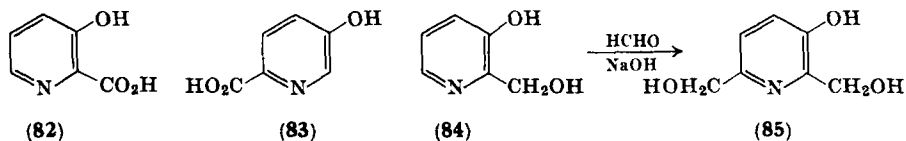
The *ortho*-Claisen rearrangement, a "no-mechanism" type of reaction, is included here since it is, effectively, an alkylation reaction though not an electrophilic substitution. Two reports have recently appeared describing the rearrangement of 2-allyloxy-pyridines in tertiary amine solvents or in the absence of a solvent. Rearrangement

¹⁷³ A. Senning, *Acta Chem. Scand.* **18**, 269 (1964).

to both the β -carbon atom and to nitrogen have been observed.^{174, 175} 4-Allyloxypyridine did not give any identifiable product.¹⁷⁴



Hydroxypyridines, in the form of their anions, undergo the Kolbe reaction with carbon dioxide under pressure. Whereas phenol gives the product of *o*-substitution, the 2-hydroxypyridine anion gives a 60% yield of the 5-carboxylic acid when heated with anhydrous potassium carbonate and carbon dioxide at 50 atm and 200°. ⁸⁹ When the sodium salt of 3-hydroxypyridine was heated *rapidly* to 280° with carbon dioxide at atmospheric pressure, the only product obtained was the 2-carboxylic acid **82** (8%). Under the same conditions, the potassium salt gave a mixture of **82** (3%) and 3-hydroxypyridine-6-carboxylic acid (**83**) (24%). When the sodium salt was heated with anhydrous potassium carbonate and carbon dioxide at 210° and 45 atm for 8–9 hours apparently only **83** was formed in high yield (85–87%).^{172, 176} These somewhat surprising results might be explicable if one assumes different degrees of anionic character of the 3-hydroxypyridine under the various conditions used. For example, it might be expected that under the first set of conditions used above the phenol was regenerated and reacted further with the carbon dioxide to give **82**. When 3-hydroxypyridine itself was heated with potassium carbonate and carbon dioxide at 250° for 8 hours, the *o*:*p*-ratio



¹⁷⁴ R. B. Moffett, *J. Org. Chem.* **28**, 2885 (1963).

¹⁷⁵ F. J. Dinan and H. Tieckelmann, *J. Org. Chem.* **29**, 892 (1964).

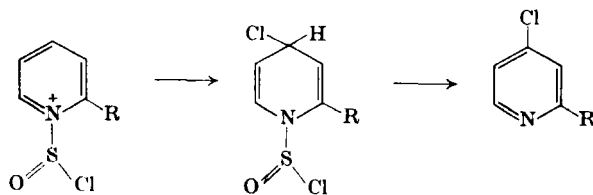
¹⁷⁶ H. Bojarska-Dahlig and T. Urbański, *Roczniki Chem.* **26**, 158 (1952); *Chem. Abstr.* **50**, 338 (1956).

(82/83) was 28:21.¹⁷⁷ The potassium salt of 3-hydroxy-2-picoline reacted with carbon dioxide in the presence of potassium carbonate at 250° and 500 psi to give a high yield (93%) of the 6-carboxylic acid.¹⁷⁸ 5-Hydroxy-3-picoline also gave a monocarboxylic acid, but the position of the carboxyl function was not established.¹⁶³ This should be readily determinable by making use of the Gibbs test for *p*-unsubstituted phenols. The 4-hydroxypyridine anion gave a 3-mono- or a 3,5-dicarboxylic acid depending on the reaction conditions.¹⁷⁹

3-Hydroxypyridine undergoes hydroxymethylation at C-2 to give **84** under basic conditions, which reacts further to give the 2,6-dihydroxymethyl derivative **85**.¹⁸⁰ 3-Hydroxypyridine derivatives also undergo the Mannich reaction, substitution taking place at the 2-position.¹⁸¹

5. Pyridinecarboxylic Acids

A carboxyl group usually hinders electrophilic attack. It is, therefore, at first sight surprising to note that picolinic acid hydrochloride reacts with thionyl chloride to give 4-chloropicolinic acid in yields of up to 55%.¹⁸²⁻¹⁸⁴ Under more severe conditions a 35% yield of 4,6-dichloropicolinic acid is obtained.¹⁸² Sulfur dioxide in the reaction mixture favors 4-chloropicolinic acid formation.¹⁸³ This suggests that the chlorination may actually involve a nucleophilic attack by chloride ion upon a complexed pyridinium salt¹:



¹⁷⁷ O. Baine, G. F. Adamson, J. W. Barton, J. L. Fitch, D. R. Swayampati, and H. Jeskey, *J. Org. Chem.* **19**, 510 (1954).

¹⁷⁸ H. Rapoport and E. J. Volcheck, *J. Am. Chem. Soc.* **78**, 2451 (1956).

¹⁷⁹ H. Bojarska-Dahlig and P. Nantka-Namirski, *Roczniki Chem.* **29**, 1007 (1955); *Chem. Abstr.* **50**, 11137 (1956).

¹⁸⁰ D. Heinert and A. E. Martell, *Tetrahedron* **3**, 49 (1958).

^{181a} A. Stempel and E. C. Buzzi, *J. Am. Chem. Soc.* **71**, 2969 (1949).

^{181b} L. D. Smirnov, V. P. Lezina, V. F. Bystrov, and K. M. Dyumaev, *Izv. Akad. Nauk SSSR, Ser. Khim.* 198 (1965); *Chem. Abstr.* **62**, 11774 (1965).

¹⁸² H. Meyer and R. Graf, *Ber.* **61**, 2202 (1928).

¹⁸³ H. S. Mosher and M. Look, *J. Org. Chem.* **20**, 283 (1955).

¹⁸⁴ R. Graf, *J. Prakt. Chem.* **133**, 36 (1932).

When nicotinic acid is heated for 8 hours at 180° with thionyl chloride, a low yield of 5-chloronicotinic acid is obtained.¹⁸² The orientation observed in this case suggests an electrophilic attack, perhaps on a complexed nicotinic acid chloride molecule (which would thus behave somewhat like a pyridine *N*-oxide). If the reaction is carried out at 150° and the reaction time lengthened to 50 hours, a 30% yield of 5,6-dichloronicotinic acid is obtained.¹⁸² Both mechanistic pathways may be involved here. Isonicotinic acid reacts with thionyl chloride at 180–220°, presumably by way of an electrophilic attack since 3-chloro- and 3,5-dichloroisonicotinic acid are formed.¹⁸² Nicotinoyl chloride (from nicotinic acid and thionyl chloride—probably in the complexed form) gives an 87% yield of 5-bromonicotinic acid on reaction with bromine for 10 hours at 150–170°.¹⁸⁵

6. Polysubstituted Pyridines

If more than one substituent is present in the pyridine nucleus, their effects are usually additive, with the “stronger,” usually activating, substituent dominating the picture. For example, *N*-methyl-3-nitro-2-pyridone undergoes nitration quite readily to give the 3,5-dinitro compound.¹²⁹ Similarly, 3,4-dicyano-6-methyl-2-pyridone is nitrated readily at C-5,¹⁸⁶ in spite of the presence of two deactivating substituents in the nucleus. 3-Bromo-5-hydroxypyridine reacts with bromine water to give the tetrabromo-3-hydroxypyridine, whereas 2-bromo-5-hydroxypyridine gives 2,4,6-tribromo-5-hydroxypyridine under these conditions.¹⁸² 3-Amino-2,4-dichloropyridine is chlorinated *para* to the activating amino group and *meta* to the deactivating halogens.¹³⁵ A large number of examples similar to the above are reported in the literature, too many to be listed here.

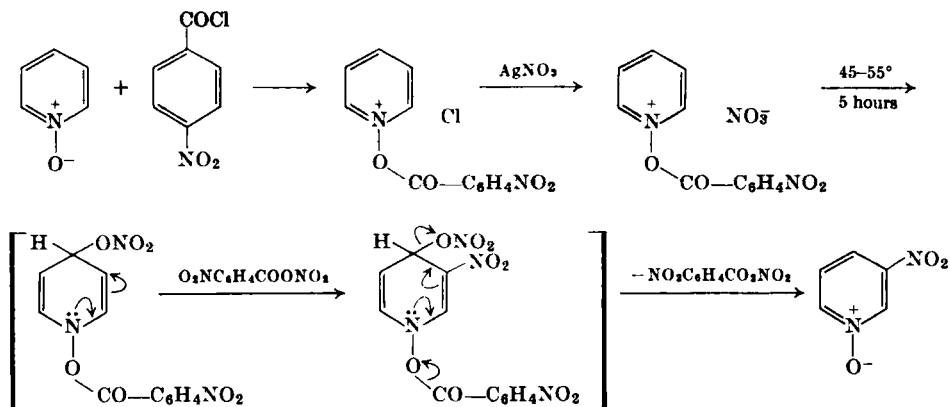
B. PYRIDINE *N*-OXIDES

As has already been mentioned in Section II, pyridine *N*-oxide is much more susceptible to electrophilic attack than is pyridine. Nitration with fuming nitric acid in sulfuric acid at 90° or with potassium nitrate or nitric acid in fuming sulfuric acid at 100–130° gives up to 90% yields of 4-nitropyridine *N*-oxide together with a small amount of the 2-isomer (formation of 2-isomer reported by

¹⁸⁵ G. B. Bachman and D. D. Micucci, *J. Am. Chem. Soc.* **70**, 2381 (1948).

¹⁸⁶ J. H. Mowat, F. J. Pilgrim, and G. H. Carlson, *J. Am. Chem. Soc.* **65**, 954 (1943).

Ochiai, reference 202). Chlorination may be effected either by heating the hydrochloride with phosphorus pentachloride at 140° , when the product is 4-chloropyridine,¹⁸⁷ or by the action of sulfuryl chloride on the *N*-oxide, when a mixture of 2-chloropyridine (57%) and 4-chloropyridine (43%) was obtained.¹⁸⁸ The observed predominant nitration at C-4 is probably more a function of the polarizability of the N—O bond resulting from contributions of structure **1d** to the species going to the transition state, and of the powerful inductive effect of the *N*-oxide function which would tend to reduce the reactivity of the 2-position toward electrophilic attack (as well as perhaps also the effect of solvation), than of steric hindrance by the oxygen atom to attack at C-2.^{1, 6} As already mentioned, nitration of pyridine *N*-oxide occurs on the free base,^{7b} while acid-catalyzed hydrogen exchange involves the conjugate acid of the base.^{7c} Nitration of pyridine *N*-oxide with benzoyl nitrate, or preferably *p*-nitrobenzoyl nitrate, yields 3-nitropyridine *N*-oxide together with a slightly larger amount of 3,5-dinitropyridine *N*-oxide and much starting material.¹⁸⁹ The proposed mechanism for this reaction is as in Scheme I.^{189, 190} A



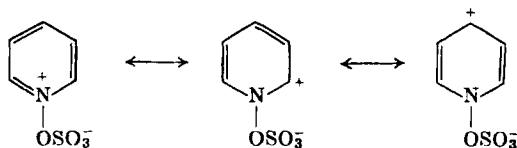
¹⁸⁷ M. Murakami and E. Matsumura, *J. Chem. Soc. Japan* **70**, 393 (1949); *Chem. Abstr.* **45**, 4698 (1950).

¹⁸⁸ B. Bobrański, L. Kochańska, and A. Kowalewska, *Ber.* **71**, 2385 (1938).

¹⁸⁹ E. Ochiai and C. Kaneko, *Chem. Pharm. Bull. (Tokyo)* **8**, 28 (1960); *Chem. Abstr.* **55**, 5491 (1961).

¹⁹⁰ E. Ochiai and C. Kaneko, *Chem. Pharm. Bull. (Tokyo)* **7**, 267 (1959).

similar mechanism has been proposed to account for the formation of a 35% yield of 3,5-dibromopyridine *N*-oxide when pyridine *N*-oxide is boiled under reflux for 3 hours with bromine, acetic anhydride, and sodium acetate in chloroform solution.¹⁹ In contrast to nitration and mercuration, both sulfonation and bromination of pyridine *N*-oxide require very vigorous conditions and proceed only in relatively low yields. For example, bromination at 200° for 20 hours in 90% sulfuric acid in the presence of silver sulfate gives a 10% yield of bromopyridine *N*-oxides ($\alpha:\gamma$ -ratio, 1:2).¹⁹¹ The *N*-oxide undergoes a 25–30% conversion into a mixture of bromo derivatives when it is heated for 10 hours at 120° with half the molar amount of bromine in 65% oleum.¹⁹² The mixture of bromination products formed consisted of ca. 60% of monobromo, ca. 35% of dibromo, and ca. 5% of tribromo derivatives. The monobromopyridine *N*-oxide fraction consisted mainly of 3-bromopyridine *N*-oxide with very minor amounts of the 2- and the 4-isomers. The dibromopyridine *N*-oxides consisted essentially of about equal amounts (15%) of 2,5- and 3,4-dibromopyridine *N*-oxide, together with a small amount (5%) of the 2,3-isomer. Interestingly, no 3,5-dibromo compound is formed. The predominant formation of product of reaction at the β -position has been explained by suggesting that in fuming sulfuric acid a complex is formed between the pyridine *N*-oxide and SO_3 , the structure of which results in the deactivation of the 2-, 4-, and 6-positions. The fact that, in spite of this, bromination proceeded more readily in this medium than in 90% sulfuric acid was attributed to the presence of bromonium ions in high concentration (cf. Arotsky *et al.*¹⁹³).



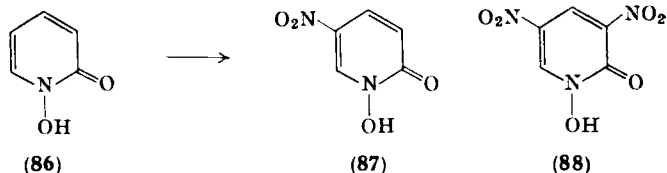
The directive influence of the *N*-oxide grouping in electrophilic substitution exceeds that of any but the most powerful *o:p*-directing groups that may also be present in the nucleus. Thus, nitration of

¹⁹¹ H. C. van der Plas, H. J. den Hertog, M. van Ammers, and B. Haase, *Tetrahedron Letters* **1961**, 32.

¹⁹² M. van Ammers, H. J. den Hertog, and B. Haase, *Tetrahedron* **18**, 227 (1962).

¹⁹³ J. Arotsky, H. C. Mishra, and M. C. R. Symons, *J. Chem. Soc.* **1961**, 12.

2-picoline *N*-oxide,^{194, 195} 3-picoline *N*-oxide,^{196, 197} 2-bromopyridine *N*-oxide,¹⁹⁵ 3-bromopyridine *N*-oxide,^{198, 199} 2-methoxypyridine *N*-oxide,²⁰⁰ 2-ethoxypyridine *N*-oxide,¹⁹⁵ 3-methoxypyridine *N*-oxide,²⁰⁰ 3-ethoxypyridine *N*-oxide,¹⁹⁵ 2-acetamidopyridine *N*-oxide,²⁰¹ 2,6-lutidine *N*-oxide,²⁰² and 3,5-dibromopyridine *N*-oxide²⁰³ gives, in every case, the 4-nitro derivative in reasonable to excellent yields. No reaction was apparently observed in the attempted nitration of 2,4,6-collidine *N*-oxide.²⁰⁴ This has now been effected.^{204a} In contrast to this, nitration of 2-hydroxypyridine *N*-oxide with nitric acid in acetic acid at 0° gave the 5-nitro compound **87** in 60–70% yield. Under more vigorous conditions the 3,5-dinitro derivative **88** was formed as well.¹⁴³ Clearly the presence of a nitro group does not seriously hinder the reaction. This has been taken as additional evidence that the starting material exists in the cyclic hydroxamic acid form (**86**) and that it is this *N*-hydroxy-2-pyridone form that is undergoing nitration. Similarly, *N*-hydroxy-4-pyridone gives 3-nitro- and 3,5-dinitro-*N*-hydroxy-4-pyridone with nitric acid in glacial acetic acid,^{205, 206}



¹⁹⁴ E. Ochiai, K. Arima, and M. Ishikawa, *J. Pharm. Soc. Japan* **63**, 79 (1943); *Chem. Abstr.* **45**, 5151 (1951).

¹⁹⁵ H. J. den Hertog, C. R. Kolder, and W. P. Combé, *Rec. Trav. Chim.* **71**, 745 (1952).

¹⁹⁶ W. Herz and L. Tsai, *J. Am. Chem. Soc.* **76**, 4184 (1954).

¹⁹⁷ E. C. Taylor, Jr. and A. J. Croveti, *Org. Syn.* **36**, 53 (1956).

¹⁹⁸ H. J. den Hertog and J. Overhoff, *Rec. Trav. Chim.* **69**, 468 (1950).

¹⁹⁹ R. Jujo, *J. Pharm. Soc. Japan* **66**, 21 (1946); *Chem. Abstr.* **45**, 6201 (1951).

²⁰⁰ H. J. den Hertog and M. van Ammers, *Rec. Trav. Chim.* **74**, 1160 (1955).

²⁰¹ E. V. Brown and P. L. Molloy, *Abstr. Papers 126th Meeting Am. Chem. Soc., New York*, 1954 p. R91.

²⁰² E. Ochiai, *J. Org. Chem.* **18**, 534 (1953).

²⁰³ H. J. den Hertog, C. H. Henkens, and K. Dilz, *Rec. Trav. Chim.* **72**, 296 (1953).

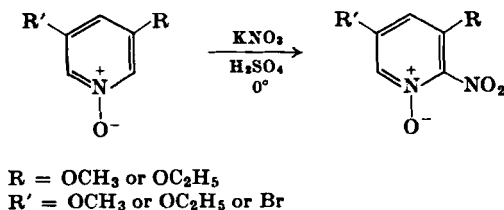
²⁰⁴ M. Ishikawa, *J. Pharm. Soc. Japan* **64**, 6 (1945); *Chem. Abstr.* **45**, 8529 (1951).

^{204a} A. R. Katritzky, Private communication (1964)

²⁰⁵ E. Hayashi, *J. Pharm. Soc. Japan* **70**, 142 (1950); *Chem. Abstr.* **44**, 5880 (1950).

²⁰⁶ E. Ochiai and K. Futaki, *J. Pharm. Soc. Japan* **72**, 274 (1952); *Chem. Abstr.* **47**, 6416 (1953).

whereas 4-acetamidopyridine *N*-oxide yields a 2-nitro derivative.²⁰¹ 2-*N'*,*N'*-Dimethylaminopyridine *N*-oxide, which cannot exist in the tautomeric *N*-hydroxy form, is nitrated at C-5.⁶² The presence of two ether groups or of one ether group and one bromine atom at C-3 and C-5 results in a change in the usual orientation, substitution now



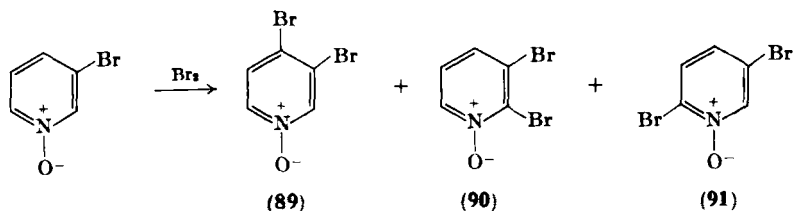
taking place at C-2.^{203, 207} For example, nitration of 5-bromo-3-methoxypyridine *N*-oxide gives an 80% yield of 5-bromo-3-methoxy-2-nitropyridine *N*-oxide, no trace of the 4-nitro compound being detected.²⁰⁷ Under more vigorous conditions the 2,6-dinitro compound is obtained. The possibility of steric hindrance to attack at C-4 has been considered to account for these observations. The formation of some 5-methyl-2-nitropyridine together with the expected 4-nitro-3-picoline *N*-oxide on nitration of 3-picoline *N*-oxide has recently been reported.^{207a}

Although the mechanism of chlorination of pyridine *N*-oxides by the action of phosphorus oxychloride, phosphorus pentachloride, or sulfuryl chloride has not been established, it seems most likely that some of these reactions involve intra- or inter-molecular attack by chloride ion or potential chloride ion following complexing at oxygen (see Sections II and IV). With a few exceptions, they are therefore more appropriately discussed under the heading of nucleophilic substitutions (Section IV, A, 3). One such exception may be the reaction of *N*-hydroxy-4-pyridone with sulfuryl chloride, which ultimately gives 1,2,2,3,3,5,6-heptachloro-2,3-dihydro-4-pyridone (65). It has been proposed that the first step in this reaction is the formation of 3,5-dichloro-*N*-hydroxy-4-pyridone.¹⁵⁷ If this is so, then it must involve electrophilic attack at the two β -positions, followed by the more usual nucleophilic substitutions.

²⁰⁷ H. J. den Hertog, M. van Ammers, and S. Schukking, *Rec. Trav. Chim.* **74**, 1171 (1955).

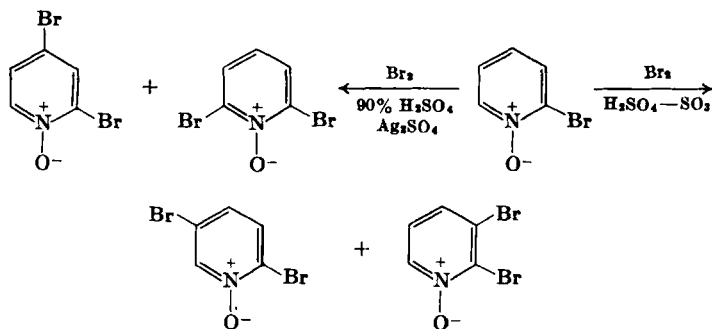
^{207a} G. M. Badger and R. P. Rao, *Australian J. Chem.* **17**, 1399 (1964).

The bromination of 3-bromopyridine *N*-oxide has been studied under two sets of conditions. With bromine in 90% sulfuric acid containing silver sulfate at 160°, bromination is very slow: after 20 hours a 5–10% over-all yield of polysubstituted products was obtained. This was found to consist of 3,4-dibromopyridine *N*-oxide (**89**) (64%), 2,3-dibromopyridine *N*-oxide (**90**) (14%), and 2,5-dibromopyridine *N*-oxide (**91**) (22%). The favored attack at C-4 is in agreement with the results obtained with pyridine *N*-oxide under these conditions. It is interesting, however, that once again no 3,5-dibromopyridine *N*-oxide is produced in this reaction. When 3-bromopyridine *N*-oxide was brominated for 10 hours in fuming sulfuric acid at 120°, the same dibromo compounds were formed in an over-all yield of 25–30%, but the isomer ratios differed appreciably. The 2,5-dibromo derivative **91** was the main product (61%), together with equal amounts (16%) of **89** and **90**. Small amounts of 2,4,5-tribromopyridine *N*-oxide (3%) and 2,3,3-tribromopyridine *N*-oxide (4%)



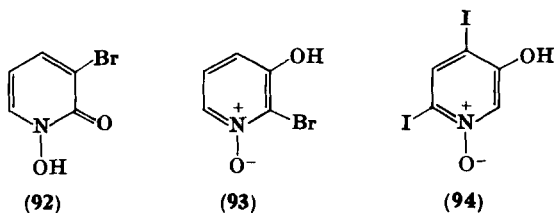
were also formed. To explain these results it was suggested that in fuming sulfuric acid the orienting effect of the bromine atom already present in the nucleus surpasses that of the complexed *N*-oxide group, the second bromine atom entering *ortho* or *para* to the first. This proposal finds some confirmation in the results obtained in the bromination of 2-bromopyridine *N*-oxide under both sets of conditions.¹⁹² The reactions are illustrated in Scheme II. The 2,4:2,6-isomer ratio in the 90% sulfuric acid reaction was 4.5:1. In the bromination in fuming sulfuric acid the effects of the bromine atom and of the $\text{N}^+-\text{OSO}_3^-$ group reinforce each other. A similar effect is observed in the bromination of 4-bromopyridine *N*-oxide in fuming sulfuric acid: the sole monosubstitution product is the 3,4-dibromo derivative (84% of total); some 3,4,5-tribromopyridine *N*-oxide (10%) is also formed.

The reaction of *N*-hydroxy-2-pyridone with bromine in acetic acid



SCHEME II

gave the 3-bromo derivative **92** (15%).²⁰⁸ With bromine water only 3,5-dibromo-*N*-hydroxy-2-pyridone was obtained.¹⁴³ 3-Hydroxypyridine *N*-oxide is said to react with bromine to give 2-bromo-3-hydroxypyridine *N*-oxide (**93**), which then reacts further to yield first the 2,6-dibromo and then the 2,4,6-tribromo compound. In contrast to this, iodination of 3-hydroxypyridine *N*-oxide results in the formation of 4,6-diiodo-3-hydroxypyridine *N*-oxide (**94**), C-2 pre-

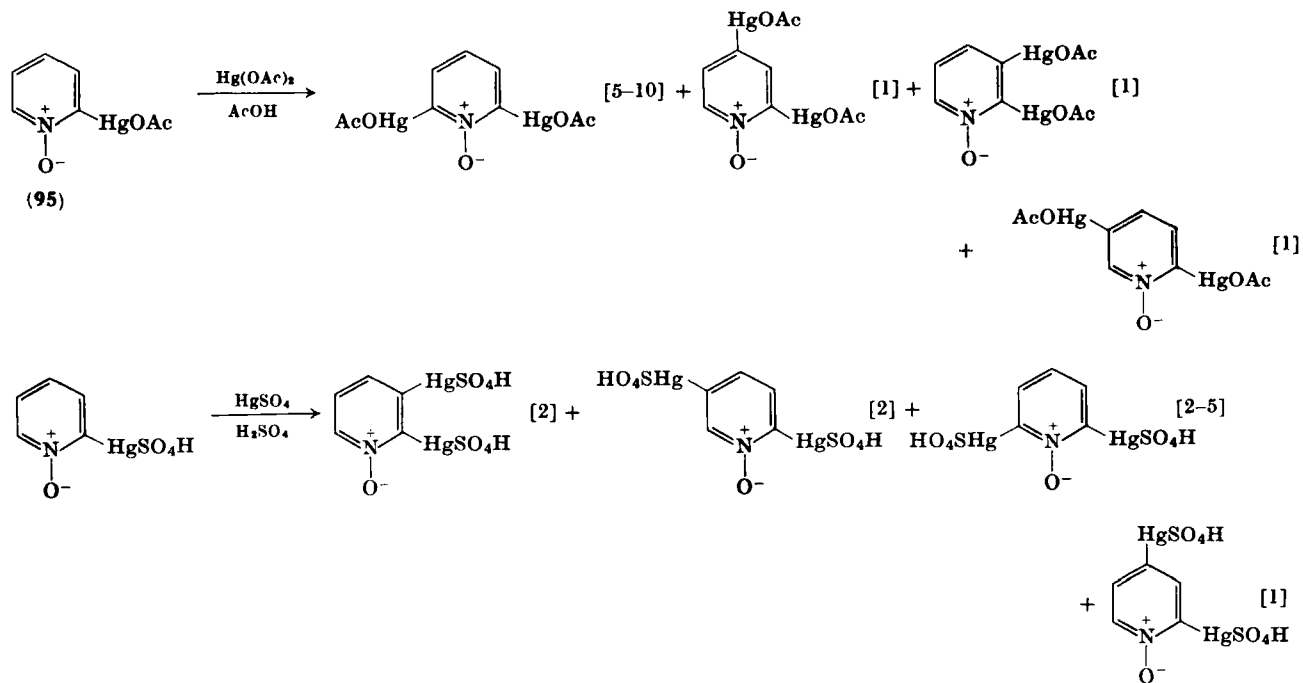


sumably remaining unsubstituted for steric reasons.⁶² *N*-Hydroxy-4-pyridone is brominated in aqueous solution to the 3,5-dibromo compound.²⁰⁹ When 4-nitropyridine *N*-oxide is heated with concentrated hydrobromic acid at 160°, electrophilic bromination apparently follows hydrolysis to the 4-pyridone: 3,5-dibromo-*N*-hydroxy-4-pyridone is evidently formed, since heating the product with phosphorus oxybromide results in 3,4,5-tribromopyridine in excellent yield.²¹⁰ A 20% yield of 3-chloro-*N*-hydroxy-4-pyridone is formed together with *N*-hydroxy-4-pyridone when 4-nitropyridine *N*-oxide is heated with 5% hydrochloric acid at 180–190°.²⁰⁹

²⁰⁸ W. A. Lott and E. Shaw, *J. Am. Chem. Soc.* **71**, 70 (1949).

²⁰⁹ H. J. den Hertog and W. P. Combé, *Rec. Trav. Chim.* **71**, 745 (1952).

²¹⁰ H. J. den Hertog and W. P. Combé, *Rec. Trav. Chim.* **70**, 581 (1951).



SCHEME III

It was initially reported²¹¹ that mercuration of pyridine *N*-oxide with mercuric acetate in glacial acetic acid at 130° gave the 4-acetoxy-mercuric compound (78% yield). This was later shown to be incorrect.^{212, 213} Under the above conditions, acetoxymercuration at C-2 occurs first to give **95**, which undergoes further substitution as shown in Scheme III (the relative amounts of products obtained are shown in brackets alongside the formulas). The orientation of the second mercuric substituent is somewhat different when the reaction is carried out with mercuric sulfate in sulfuric acid, more attack at C-3 taking place than before. Presumably, in the strong acid used, the *O*-protonated form of the *N*-oxide is making a greater contribution to orientation.²¹³

Sulfonation of pyridine *N*-oxide requires the use of 20% fuming sulfuric acid and a mercuric sulfate catalyst with prolonged heating at 230°. Under these conditions, the main product is the 3-sulfonic acid (40–45%) together with small amounts of the 2- (0.5–1%) and 4-sulfonic acids (2–2.5%).²¹⁴ 2,6-Lutidine *N*-oxide reacts under similar conditions, substitution taking place at C-3.²¹⁵

IV. Nucleophilic Substitution

A. ADDITION–ELIMINATION MECHANISM

1. *Pyridines*

In contrast to the electrophilic replacement of a proton, nucleophilic attack upon the pyridine nucleus often takes place with ease, and eventual displacement of a hydride ion results if a powerful enough nucleophile is used. Such reactions generally occur in two stages. First, there is the addition stage, which produces the usually negatively charged σ -complex. This may be very unstable under the conditions or, given the proper incentive, go on to product without accumulating, so that at all times it is only present in small concentrations. Alternatively, and in a number of cases, a relatively stable intermediate can be formed, and higher temperatures or oxidizing agents

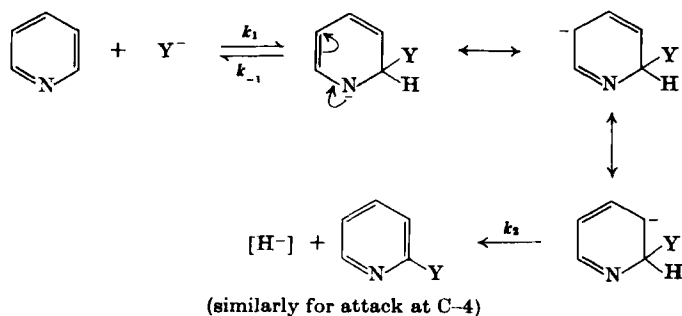
²¹¹ T. Ukai, Y. Yamamoto, and S. Hirano, *J. Pharm. Soc. Japan* **73**, 823 (1953); *Chem. Abstr.* **48**, 9946 (1954).

²¹² M. van Ammers and H. J. den Hertog, *Rec. Trav. Chim.* **77**, 340 (1958).

²¹³ M. van Ammers and H. J. den Hertog, *Rec. Trav. Chim.* **81**, 124 (1962).

²¹⁴ M. van Ammers and H. J. den Hertog, *Rec. Trav. Chim.* **78**, 586 (1959).

²¹⁵ R. F. Evans and H. C. Brown, *J. Org. Chem.* **27**, 1329 (1962).



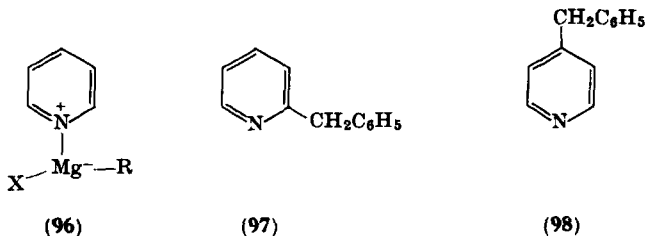
may have to be supplied to cause the elimination of a hydride ion, thus taking the reaction to completion.

Among the powerful nucleophilic reagents that have been used to effect substitution in pyridine and its derivatives, the most studied are the alkali metal amides (the Tschitschibabin reaction), the Grignard reagents, and the organolithium compounds. Weaker nucleophiles such as the hydroxide ion and some carbanions have also been used. The bonding of still weaker nucleophiles such as cyanide or halide ions requires a lower electron-density than is present in the pyridine nucleus itself so that such reactions have been encountered only with quaternary pyridinium salts and *O*-alkylated *N*-oxides. It should again be borne in mind, however, that even the reactions with strong reagents probably involve, at some stage, complexing at nitrogen with a metal atom so that it would be incorrect to regard such reactions as typical of the neutral pyridine molecule (if such a species does exist as such other than in the gaseous or pure state).

Relatively few reactions of Grignard reagents with pyridine and its derivatives have been studied. This is probably due to the fact that these reagents are less powerful nucleophiles than the corresponding organolithium compounds and hence require more vigorous conditions to effect substitution than do the latter, which have found many more synthetic applications in this series. Also, the orientation of the entering alkyl or aryl group has not always been unambiguously established. In contrast to what is usually observed with organolithium compounds, substitution by Grignard reagents can take place at either the α - or the γ -position, or at both. This reaction was first studied by Bergstrom and McAllister,²¹⁶ who found that pyridine and Grignard reagents form complexes (probably having the structure **96**)

²¹⁶ F. W. Bergstrom and S. H. McAllister, *J. Am. Chem. Soc.* **52**, 2845 (1930).

in the cold; these, on heating in diethyl ether solution in an autoclave at 150–160°, rearrange to alkyl- or arylpyridines. Thus, ethylmagnesium bromide and phenylmagnesium bromide were said to give 2-ethyl- and 2-phenylpyridine, respectively, in reasonably good yield (44–45%). The formation of 2-ethylpyridine in this reaction has been seriously questioned,²¹⁷ since the melting point of the picrate of the product obtained (m.p. 187–189°) differs appreciably from that of 2-ethylpyridine (m.p. 108–109°) prepared by an unambiguous method. It has been suggested that dipyridyls are formed under these conditions. On the other hand, both the nitrogen analysis results for the picrate and the melting point of the auric chloride double salt of the



base prepared by the Grignard reaction agree with those expected for 2-ethylpyridine.²¹⁶ A solution of ether-free *n*-butylmagnesium iodide in toluene reacted with pyridine under reflux to give 2-*n*-butylpyridine (18%) essentially free from 4-isomer.²¹⁸ Nicotine and 2-picoline were reported to react with ethylmagnesium bromide, but the products were not characterized.²¹⁶ Pyridine and *s*-butylmagnesium bromide gave a mixture of 2-*s*-butylpyridine (5.8%) and 4-*s*-butylpyridine (3.3%).²¹⁹ The reaction of dibenzylmagnesium or of benzylmagnesium chloride was said to give 2-benzylpyridine (97).²²⁰ This, too, has been disputed,²²¹ the product being said to be 4-benzylpyridine (98). A subsequent study of the reaction with benzylmagnesium chloride by Benkeser and Holton²²² has shown that both 97 and 98 are formed in yields of 20 and 80%, respectively. Allyl-

²¹⁷ N. Goetz-Luthy, *J. Am. Chem. Soc.* **71**, 2254 (1949).

²¹⁸ D. Bryce-Smith, P. J. Morris, and B. J. Wakefield, *Chem. Ind. (London)* **1964**, 495.

²¹⁹ W. von E. Doering and V. Z. Pasternak, *J. Am. Chem. Soc.* **72**, 143 (1950).

²²⁰ E. Bergmann and W. Rosenthal, *J. Prakt. Chem.* **135**, 267 (1932).

²²¹ W. L. C. Veer and S. Goldschmidt, *Rec. Trav. Chim.* **65**, 793 (1946).

²²² R. A. Benkeser and D. S. Holton, *J. Am. Chem. Soc.* **73**, 5861 (1951).

magnesium bromide and pyridine give 4-allylpyridine exclusively.²²³ Nicotinonitrile and propylmagnesium bromide gave 3-butyryl-4-propylpyridine.²²⁴ The direct 4-alkylation of pyridine using a mixture of the alkyl (or aryl) chloride, magnesium powder, and pyridine at 120° has been achieved. Only small quantities of the 2-isomer were formed.²¹⁸ This reaction cannot involve the formation of the Grignard reagent followed by alkylation. While a number of mechanisms come to mind, further work is necessary before one is proposed. In the light of the foregoing discussion, it is not surprising that the reaction of Grignard reagents with substituted pyridines has not been studied systematically. With the modern analytical techniques available, such a study should lead to interesting results, particularly when these are contrasted with the data being accumulated on the reactions using organolithium derivatives.

If suitable electron-attracting substituents, capable of delocalizing a negative charge, are present in the nucleus, the intermediate resulting from the addition of the Grignard reagent may be stabilized and the dihydropyridine formed by treating the intermediate with acid isolated. 3,5-Dicyanopyridine derivatives are particularly suitable substrates, as some recent studies have shown.²²⁵⁻²²⁷ For example, 3,5-dicyanopyridine (**99**, R = H) reacts with methylmagnesium iodide in ether to give a 10% yield of 3-acetyl-5-cyanopyridine (**100**, R = H), together with a 90% yield of dihydrodicyanomethylpyridines consisting of two parts 3,5-dicyano-1,2-dihydro-2-methylpyridine (**101**, R = H) to one part 3,5-dicyano-1,4-dihydro-4-methylpyridine (**102**, R = H). Similarly, 2-methyl-3,5-dicyanopyridine (**99**, R = CH₃) gave **100** (R = H) (5%), together with **101** (R = CH₃) and **102** (R = CH₃) in the ratio of 3:1.²²⁷ Attack at C-2 clearly predominates over attack at C-4 in these additions. Similar results have been reported with ethylmagnesium bromide.²²⁵

The reaction of organolithium compounds with pyridines, discovered initially by Ziegler and Zeiser²²⁸ has been investigated much

²²³ H. Gilman, J. Eisch, and T. Soddy, *J. Am. Chem. Soc.* **79**, 1245 (1957).

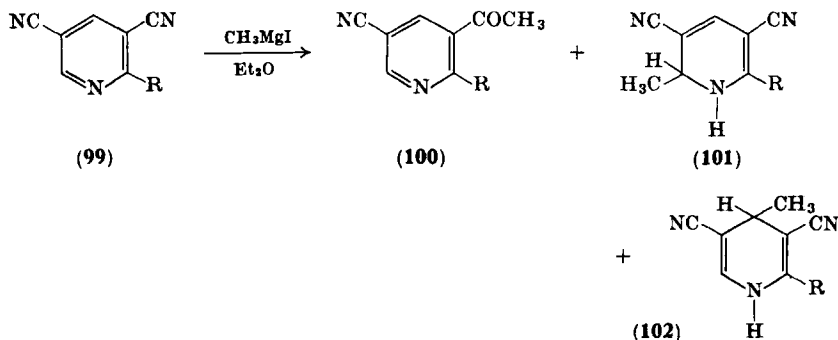
²²⁴ R. L. Frank and C. Weatherbee, *J. Am. Chem. Soc.* **70**, 3482 (1948).

²²⁵ R. Lukeš and J. Kuthan, *Angew. Chem.* **72**, 919 (1960).

²²⁶ R. Lukeš and J. Kuthan, *Coll. Czech. Chem. Commun.* **26**, 1422 and 1845 (1961).

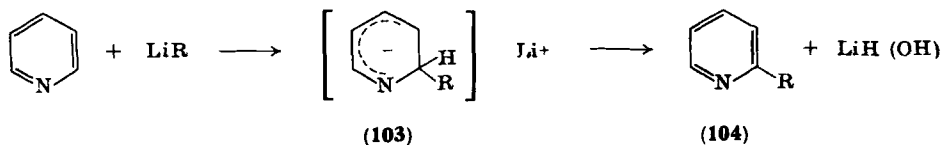
²²⁷ J. Kuthan, E. Janečková, and M. Havel, *Coll. Czech. Chem. Commun.* **29**, 143 (1964).

²²⁸ K. Ziegler and H. Zeiser, *Ber.* **63**, 1847 (1930).



more extensively, from the point of view of mechanism as well as from that of the effect of substituents upon orientation in nucleophilic aromatic substitution reactions involving the displacement of hydride ion. While much is known concerning the effect of substituents upon the susceptibility to nucleophilic attack of carbon atoms bearing halogen (or pseudo-halogen) atoms—and hence necessarily involving substitution at a *given position* in the aromatic nucleus—and in contrast to the situation existing in electrophilic aromatic substitution reactions, little was known of the effect of substituents upon orientation and the ease of replacement of a hydride ion. Unsymmetrically substituted, e.g., 3-substituted, pyridines provide good substrates for such investigations, and recent mechanistic studies have concentrated upon their use.

The reaction of a lithium alkyl or aryl with dry pyridine involves the formation of a dihydro derivative (**103**) which, on heating or on being oxidized with molecular oxygen in the cold, furnishes the 2-substituted pyridine **104**. Alternatively, **103** may be treated with water to give the 1,2-dihydro derivative which is converted to **104** by oxidation with picric acid (in which case the picrate of **104** is the product isolated) or with chloranil.²²⁹ No 4-phenylpyridine could be detected by gas chromatography in the reaction with phenyllithium.²³⁰ Support for



²²⁹ R. A. Abramovitch and C. S. Giam, *Can. J. Chem.* **41**, 3127 (1963).

²³⁰ R. A. Abramovitch and C. S. Giam, *Can. J. Chem.* **40**, 231 (1962).

the intermediacy of the species **103** has recently been adduced from the observation²³¹ that oxidation of the pyridine-phenyllithium adduct (**103**, R = C₆H₅) with benzophenone gave what is probably

TABLE III
REACTIONS OF ALKYL- AND ARYLLITHIUM DERIVATIVES WITH SOME
2- OR 4-SUBSTITUTED PYRIDINES

| Substituent | Reagent and conditions | Products | Reference ^a |
|--|---|---|------------------------|
| 2-CH ₃ | C ₆ H ₅ Li | 2-Picolylithium | 232, 233 |
| 4-CH ₃ | 4-Picoline added to C ₆ H ₅ Li | 2-Phenyl-4-picoline (39%) and 2,6-diphenyl-4-picoline (33%) | 234 |
| 4-CH ₃ | C ₆ H ₅ Li added to 4-picoline | 4-Picolylithium | 235 |
| 2- <i>n</i> -C ₄ H ₉ | <i>n</i> -C ₄ H ₉ Li | 2,6-Di- <i>n</i> -butylpyridine | 232 |
| 2- <i>t</i> -C ₄ H ₉ | <i>t</i> -C ₄ H ₉ Li | 2,6-Di- <i>t</i> -butylpyridine | 27 |
| 4-OC ₂ H ₅ | <i>t</i> -C ₄ H ₉ Li | 2- <i>t</i> -Butyl-4-ethoxy-pyridine | 236 |
| 4-OC ₂ H ₅ -2- <i>t</i> -C ₄ H ₉ | <i>t</i> -C ₄ H ₉ Li | 2,6-Di- <i>t</i> -butyl-4-ethoxy-pyridine | 236 |
| 4-SCH ₃ | <i>t</i> -C ₄ H ₉ Li | 2- <i>t</i> -Butyl-4-methylmercaptopyridine | 236 |
| 2- <i>t</i> -C ₄ H ₉ -4-SCH ₃ | <i>t</i> -C ₄ H ₉ Li | Di-4-(2,6-di- <i>t</i> -butylpyridyl)disulfide (major) and di-4-(2,6-di- <i>t</i> -butylpyridyl)sulfide (minor) | 236 |
| 2-(2,5-Dimethyl-1-pyrryl) | <i>p</i> -(CH ₃) ₂ NC ₆ H ₄ Li | 2- <i>p</i> -Dimethylamino-phenyl-6-(2',5'-dimethylpyrryl)-pyridine | 237 |

^a See footnotes.

²³¹ R. A. Abramovitch and B. Vig, *Can. J. Chem.* **41**, 1961 (1963).

²³² K. Ziegler and H. Zeiser, *Ann.* **485**, 174 (1931).

²³³ L. A. Walter, *Org. Syn.* **23**, 83 (1943).

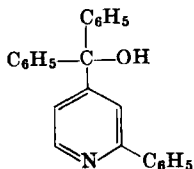
²³⁴ C. Osuch and R. Levine, *J. Am. Chem. Soc.* **78**, 1723 (1956).

²³⁵ J. P. Wibaut and J. W. Hey, *Rec. Trav. Chim.* **72**, 513 (1953).

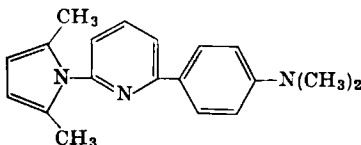
²³⁶ H. C. van der Plas and H. J. den Hertog, *Rec. Trav. Chim.* **81**, 841 (1962).

²³⁷ H. Gilman, C. G. Stuckwisch, and J. F. Nobis, *J. Am. Chem. Soc.* **68**, 326 (1946).

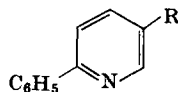
4-diphenylhydroxymethyl-2-phenylpyridine (105). This could arise by the addition of the 2-phenyl-1,2-dihydropyridyllithium intermediate to benzophenone followed by oxidation and a molecular rearrangement.



(105)



(106)



(107)

The results of the reactions of a variety of lithium organometallics with some 2- and 4-substituted pyridines are summarized in Table III. The formation of a 4-substituted pyridine, with one exception, has not been reported in such reactions except in those cases where the 2- and 6-positions of the pyridine ring are blocked, e.g., the case of acridine.²³⁸ Benzyllithium is said to react with pyridine to give 4-benzylpyridine (17%).²³⁹ We are clearly dealing here with the reaction of a relatively stable anion (see subsequent discussion). When the Ziegler alkylation is carried out as a one-step process, namely by reacting together lithium, a halide, and pyridine, the corresponding 4-substituted pyridine is obtained in place of the expected 2-isomer, although only in 10% yield. The mechanism of this reaction must differ from that involving the addition of the preformed alkylolithium to pyridine, which gives only the 2-isomer.²¹⁸

The orientation in the reaction of organolithium compounds with 3-substituted pyridines had not always been unambiguously established. For example, it was reported that 3-picoline and phenyllithium combined to give 5-methyl-2-phenylpyridine (107, R = CH₃) exclusively.²⁴⁰ This has been shown to be quite the opposite of what actually happens²⁴¹ (see Table IV). Similarly, 3-phenylpyridine was said to

²³⁸ E. Bergmann, O. Blum-Bergmann, and A. F. von Christiani, *Ann.* **483**, 80 (1930).

²³⁹ H. Gilman and H. A. McNinch, *J. Org. Chem.* **27**, 1889 (1962).

²⁴⁰ A. D. Miller, C. Osuch, N. N. Goldberg, and R. Levine, *J. Am. Chem. Soc.* **78**, 674 (1956).

²⁴¹ R. A. Abramovitch, C. S. Giam, and A. D. Notation, *Can. J. Chem.* **38**, 761 (1960).

give only 2,5-diphenylpyridine (**107**, $R = C_6H_5$) with C_6H_5Li ,²⁴² which was in marked contrast with the observation by Leonard and Ryder that *n*-butyllithium and 3-picoline produced predominantly 2-butyl-3-methylpyridine.²⁴³ It has now been shown that some 2,3-diphenylpyridine is also formed in the reaction of phenyllithium with 3-phenylpyridine, although **107** ($R = C_6H_5$) is the predominating isomer.²⁴⁴ Table IV summarizes the results of *quantitative analyses* of isomer ratios of products formed in the reaction of organolithium

TABLE IV
REACTION OF ALKYL- AND ARYLLITHIUM COMPOUNDS WITH 3-SUBSTITUTED
PYRIDINE DERIVATIVES (**108**)

| R in 3-R-pyridine (108) | R'Li | Per cent Composition | | Reference ^a |
|--|--------------------------------------|------------------------------|------------------------------|------------------------|
| | | 2,3-Isomer (109) | 2,5-Isomer (110) | |
| CH ₃ | C ₆ H ₅ Li | 95 | 5 | 230, 241 |
| CH ₃ | CH ₃ Li | 89 | 11 | 245 |
| CH ₃ | C ₂ H ₅ Li | 78 | 22 | 245 |
| CH ₃ | (CH ₃) ₂ CHLi | 34 | 66 | 245 |
| C ₂ H ₅ | C ₆ H ₅ Li | 84 | 16 | 230 |
| C ₂ H ₅ | CH ₃ Li | 87 | 13 | 245 |
| (CH ₃) ₂ CH | C ₆ H ₅ Li | 70 | 30 | 230 |
| (CH ₃) ₂ CH | CH ₃ Li | 69 | 31 | 245 |
| (CH ₃) ₃ C | C ₆ H ₅ Li | 4.5 | 95.5 | 230 |
| (CH ₃) ₃ C | CH ₃ Li | 1 | 99 | 245 |
| C ₆ H ₅ | C ₆ H ₅ Li | 16.5 | 83.5 | 244 |
| <i>N</i> -Methylpyrrolidyl | C ₆ H ₅ Li | 30 | 70 | 246a |
| OCH ₃ | C ₆ H ₅ Li | 100 | 0 | 246 |
| NH ₂ | C ₆ H ₅ Li | 100 | 0 | 246 |
| SO ₂ N(C ₂ H ₅) ₂ | C ₆ H ₅ Li | 100 | 0 | 244 |

^a See footnotes.

²⁴² R. H. Wiley, C. H. Jarboe, P. X. Callahan, and J. T. Nielsen, *J. Org. Chem.* **23**, 780 (1958).

²⁴³ N. J. Leonard and B. L. Ryder, *J. Org. Chem.* **18**, 598 (1953).

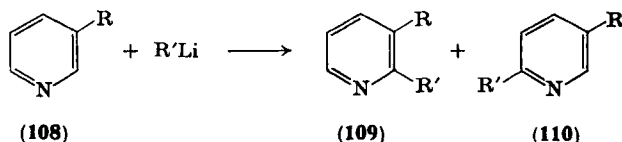
²⁴⁴ R. A. Abramovitch, K. S. Ahmed, and C. S. Giam, *Can. J. Chem.* **41**, 1752 (1963).

²⁴⁵ H. C. Brown and H. E. Podall, Private communication (1960).

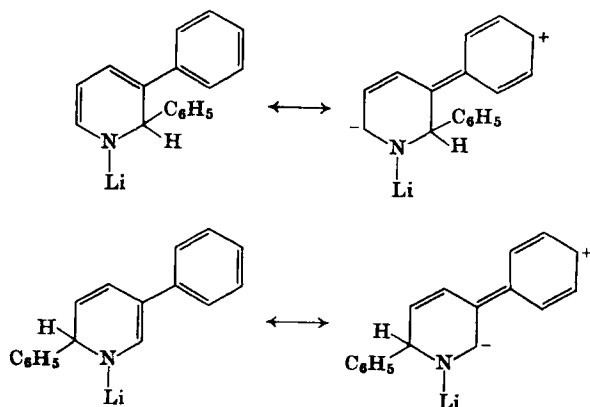
²⁴⁶ R. A. Abramovitch and A. D. Notation, *Can. J. Chem.* **38**, 1445 (1960).

^{246a} R. A. Abramovitch and G. A. Poulton, Unpublished results (1965).

compounds with 3-substituted pyridines (108) \rightarrow (109) + (110). Again (with one possible exception to be mentioned later), no products of attack at the γ -position could be detected.

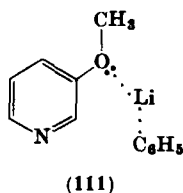


The results given in Table IV indicate that, unless a very large substituent is present at the pyridine β -position, steric hindrance by a 3-substituent to attack at C-2 appears to be small. Thus, on going from 3-methyl to 3-isopropylpyridine the 2,3-:2,5-isomer ratio falls from 95:5 to 70:30. (As will be discussed later, other factors are also involved in this decrease in isomer ratio.) The *N*-methylpyrrolidyl group in nicotine is apparently bulky enough to cause an appreciable change in the relative orientation whereas, quite unexceptionally, a *t*-butyl group exerts a much larger steric effect, thus causing a complete reversal in the preferred site of attack by the carbanion. A phenyl group is believed to be intermediate in size between ethyl and isopropyl.²⁴⁷ The 2,3-:2,5-isomer ratio of 16:84 observed in the phenylation of 3-phenylpyridine has been rationalized on the assumption that there is appreciable steric hindrance to coplanarity in the formation of the 2,3-isomer, thus favoring the production of 2,5-diphenylpyridine.



²⁴⁷ E. L. Eliel and M. N. Rerick, *J. Am. Chem. Soc.* **82**, 1367 (1960).

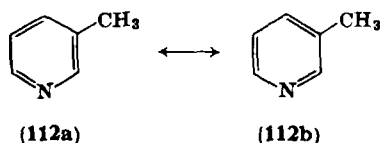
Indirect support for this hypothesis has now been obtained. Phenylation of 3-cyclohexylpyridine with phenyllithium gave a 2,3-/2,5-isomer ratio of 65:35.^{246a} The cyclohexyl radical is expected to be at least as bulky as a phenyl radical. The exclusive formation of the 2,3-isomer in the reaction of phenyllithium both with 3-amino- and 3-methoxy-pyridine has been attributed to the formation of a complex such as **111** between the lone-pair of electrons on the 3-substituent and the lithium atom, in which the phenyl group would be suitably



oriented for attack at the 2-position. This, coupled with the already established tendency for preferential addition to C-2, would account for the observed stereo-specificity. It has been suggested on the basis of these and other results, particularly with the 3-alkylpyridines, that in the transition state leading to the formation of the dihydro derivative the attacking alkyl or aryl group is almost perpendicular to the pyridine ring, whose ground state configuration is only slightly distorted.²³⁰ Thus, in spite of the greater deactivating influence due to the positive inductive effect (+I) of the alkyl group on the 2- than on the 6-position and some steric hindrance to attack at the 2-position, addition of the nucleophilic reagent takes place preferentially at that carbon atom and, in the case of a 3-methyl substituent, the *ortho:para* ratio is as high as 19. This “*ortho*” effect is reminiscent of those encountered in electrophilic substitutions of benzene derivatives bearing substituents such as NO₂, CO₂H, and CN, and of pyridine derivatives having an electron-donating 3-substituent (see Section III).

On the basis that the transition state for the addition step is as pictured above, it would be expected that the preferential orientation of the entering nucleophile would follow the order of the ground-state π -electron densities. Molecular orbital calculations of the π -electron densities at the various nuclear carbon atoms in the ground-state of 3-picoline for several different values of the nitrogen and methyl group

inductive parameters^{230, 248} indicated that the 2-position would be slightly more favorable than position 6 for nucleophilic attack only if a negative inductive effect ($-I$) was attributed to the methyl group. The introduction of methyl hyperconjugation into the ground-state calculations made little difference to the results. That the methyl group is actually exerting its usual $+I$ effect was confirmed by the NMR spectrum of 3-picoline and that of its zinc chloride complex.²⁴⁹ Another possible explanation for the orientation observed with the 3-alkylpyridines is similar to that suggested by Ingold to account for the predominant nitration of, say *m*-nitroanisole in the 2-position (see Section III, A, 3). If, of the two canonical structures (**112a** \leftrightarrow **112b**) for 3-picoline, one assumes that the electronic effect of the 3-methyl group is such as to stabilize structure **112a** with respect to **112b**, then



the former would have a larger coefficient than the latter in the aromatic wave function, and the direction of a polar effect would be that which **112a** would favor. If one then also assumes that the nucleophile will add to that end of the conjugated system whose other end is the nitrogen atom, then addition should take place preferentially at C-2.²⁵⁰ It is not clear, however, how an alkyl group would favor the stabilization of **112a** with respect to **112b**.

There is no doubt that in these reactions the nitrogen atom of the pyridine ring is complexed with either the lithium alkyl or aryl or with the lithium bromide which is usually present in many preparations of organolithium compounds. It has been established that, either in the presence of an excess of lithium bromide or in the total absence of this salt, phenyllithium still gives the same *ortho:para* ratio on reaction with 3-picoline.²²⁹ To account for the predominant formation of the 2,3-isomer in the reaction of CH_3Li with 3-alkylpyridines, it was suggested²⁵¹ that the transition states for these reactions were similar

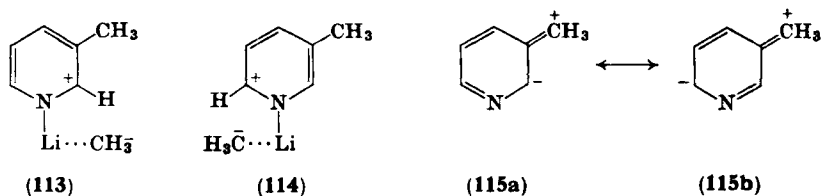
²⁴⁸ J. Ploquin, *Bull. Soc. Chim. France* **15**, 640 (1948).

²⁴⁹ R. A. Abramovitch, D. J. Kroeger, and B. Staskun, *Can. J. Chem.* **40**, 2030 (1962).

²⁵⁰ C. K. Ingold, Private communication (1959).

²⁵¹ M. S. Howie, Ph.D. Thesis, Purdue University (1961).

to **113** and **114**, and that, of the two, **113** was the more stable due to the +I effect of the alkyl group in the 3-position. A number of objections to this argument have been put forward.^{230, 244, 252} For example, there is evidence in the literature to indicate that formation of a complex



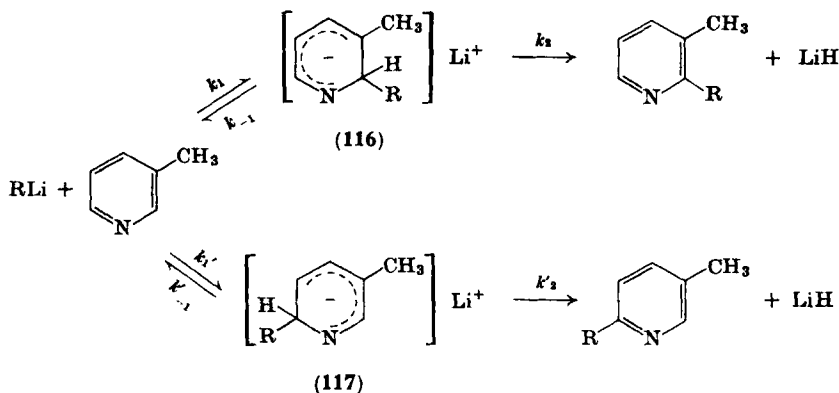
such as **113** is not a prerequisite for the observation of preferential attack at C-2. Thus, in the reaction of 3,4-lutidine methiodide with benzylmagnesium bromide, the only isomer apparently formed was the 1,2-dihydro derivative.²⁵³ Other examples of such reactions are known and are summarized in Section IV, A, 2. Clearly, further coordination at nitrogen is not possible in these cases. It has also been shown (see below) that, although the reactivity of 3-picoline relative to that of pyridine is affected by the presence or absence of lithium bromide (which forms complexes with both bases and also with phenyllithium), the 2,3-:2,5-isomer ratio is unchanged. The +I effect of the 3-methyl group acting upon transition states such as **113** and **114** cannot account for the observed activation of C-2 (see below).²⁵² Finally, in the reaction of 2-bromo-3- and -5-methylpyridine with methoxide ion in methanol, in which a cyclic transition state of the type depicted in **113** cannot be involved, kinetic studies have shown that the 2,3-isomer reacts faster than the 2,5-isomer.¹⁰ As already mentioned, the relative contributions to the ground state of hyperconjugated structures such as **115a** and **b** can hardly account for the large *ortho*:*para* ratio observed.

If the elimination of hydride ion is rate-determining and it is assumed that the addition step is rapidly reversible, the results might be explained as follows (Scheme IV), taking 3-picoline as an example: The aromatization step in Scheme IV probably involves the abstraction by the lithium cation of the hydrogen atom with its bonding pair of electrons, so that an electron-repelling *ortho*-methyl should lower the activation energy of such a process more than a *para*-methyl

²⁵² R. A. Abramovitch and C. S. Giam, *Can. J. Chem.* **42**, 1627 (1964).

²⁵³ E. L. May and E. M. Fry, *J. Org. Chem.* **22**, 1366 (1957).

group. On the other hand, if the transition state for this step resembles product, there might be appreciable 1,2-alkyl:R repulsion in the case of **116**→product but not in that of **117**→product. Thus, if the former effect is greater than the steric repulsion, k_2 would be greater than k'_2 and more 2,3-isomer would be formed than 2,5-isomer even though the equilibrium constant $K'_1 = (k'_1/k'_{-1})$ were greater than K_1 . This possible explanation has been tested in a variety of ways and the conclusion was reached that the hydride ion elimination stage in these nucleophilic aromatic substitutions is *not* important in determining the observed orientation, and that the addition stage is either virtually irreversible or the equilibrium lies far on the product side and is not rapidly reversible.²²⁹ For example, use of 3-picoline-2d in the reaction with phenyllithium gave the same 2,3-:2,5-isomer ratio as when 3-picoline itself was used. These results, incidentally, also eliminate the unlikely intervention of a "1,2-pyridyne" intermediate of the type that has been suggested^{253a} in another connection.



SCHEME IV

Two further possibilities considered were: (i) some form of steric acceleration (with the transition state for the addition step pictured above, the hydrogen atom would just begin to be moving out of the plane of the ring while the attacking nucleophile would be almost perpendicular to the ring) favoring substitution at the 2- and not at the 6-position (complexing of the nitrogen atom in the pyridine either with phenyllithium or with lithium bromide would give rise to the

^{253a} H. C. van der Plas, *Tetrahedron Letters*, 355, (1965).

same steric effect as would a conventional substituent on nitrogen); and (ii) some form of attractive interaction, perhaps of the nature of London dispersion forces, between the polarizable approaching nucleophile and the methyl substituent which would accelerate attack *ortho* to the methyl group rather than *para* to it. Dipolar field effects have been suggested to explain the high *ortho:para* ratios observed in some electrophilic substitutions.²⁵⁴ The existence of London attractive forces has been postulated to account for the accelerated rates of reaction of certain activated aryl halides in which the halogen is *ortho* to a methyl group and is substituted by a highly polarizable nucleophile.^{255, 256} The orientation might then be due not to a greater *deactivation* of the *para* than of the *ortho* position by the alkyl group but to a specific *activation* of the 2-position, the *para* position being deactivated in the usual way. This has now been shown to be the case.

The relative reactivities of pyridine, 3-picoline, and 3-ethylpyridine toward phenyllithium have been measured under various conditions by a competitive technique and found to be in the order: 3-picoline > pyridine > 3-ethylpyridine.²⁵² By carrying out reactions using an equimolar mixture of pyridine and 3-picoline and a large excess of phenyllithium, it has been possible to obtain yields of the phenylpyridines of over 80%, provided short reaction times and low temperatures are used. It has also been shown that the low yields usually obtained in such reactions are due to the fact that the dihydropyridyllithium intermediates form by-products, probably by polymerization (the intermediate dihydropyridine is a *cis*-butadiene-like system and, in the presence of a Ziegler-type catalyst, can be expected to polymerize readily). The σ -complexes from 3-picoline and phenyllithium polymerize faster than that from pyridine and phenyllithium, but there is no *selective* removal of the isomeric dihydropicolylithium intermediates to form by-products, both isomers undergoing side-reactions at virtually the same rate.

Under strictly competitive conditions using an excess of equimolar mixtures of pyridine and 3-picoline, pyridine and 3-ethylpyridine, and 3-picoline and 3-ethylpyridine and a small amount of phenyllithium in the presence or absence of lithium bromide, the isomer ratios obtained may be used to calculate total rate ratios $\frac{\bar{X}}{\bar{H}}K$ and partial rate

²⁵⁴ G. S. Hammond, in "Steric Effects in Organic Chemistry" (M. S. Newman, ed.), pp. 176-182. Wiley, New York, 1956.

²⁵⁵ J. D. Reinheimer and J. F. Bunnett, *J. Am. Chem. Soc.* **81**, 315 (1959).

²⁵⁶ J. F. Bunnett and J. D. Reinheimer, *J. Am. Chem. Soc.* **84**, 3284 (1962).

factors XF_2 and XF_6 for attack at the 2- and the 6-positions in the substituted pyridine compared with the rate of attack at C-2 of pyridine itself. Results obtained from reactions carried out under identical conditions are summarized in Table V. For the reaction with

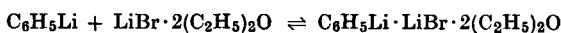
TABLE V
RELATIVE REACTIVITIES OF PYRIDINE, 3-PICOLINE, AND
3-ETHYLPYRIDINE TOWARD PHENYLLITHIUM^{a, b}

| | Pyridine and 3-picoline | Pyridine and 3-ethylpyridine | 3-Picoline and 3-ethylpyridine |
|----------------------|---|---------------------------------------|-----------------------------------|
| Total rate ratios | $\frac{CH_3}{H}K = 1.30$ | $\frac{Et}{H}K = 0.79$ | $\frac{CH_3}{Et}K = 1.80$ |
| Partial rate factors | $^{CH_3}F_2 = 2.4$ $^{CH_3}F_6 = 0.13$ | $^{Et}F_2 = 1.4$ $^{Et}F_6 = 0.16$ | — — |

^a Phenyllithium (0.0032 mole) was added to the pairs of pyridines (0.03 mole of each) at 24°. Oxygen was passed into the mixtures after they had been stirred at that temperature for 1 hour.

^b From Abramovitch and Giam.²⁵²

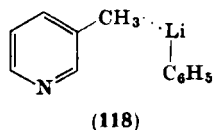
pyridine and 3-picoline, the value of the total rate ratio was confirmed²⁵² by the analysis of recovered starting materials, which led to $\frac{CH_3}{H}K = 1.3$. In the presence of an excess of lithium bromide, values of $^{CH_3}F_2 = 3.8$ and $^{CH_3}F_6 = 0.24$ were found. The increased selectivity of the phenylating agent was thought²⁵² to be due to complexing of lithium bromide etherate with phenyllithium.²⁵⁷



In all the above cases, C-2 is activated toward attack by phenyllithium compared with the same position in pyridine, while C-6 is about six- to sevenfold deactivated by the 3-methyl or 3-ethyl group compared with the α -position of pyridine. Also, the 2,3-:2,5-isomer ratios remained unchanged in all cases. A 3-methyl group activates C-2 more than does a 3-ethyl, the activation in the former case being sufficient to overcome the deactivation of C-6 and resulting in an over-all activation of the 3-picoline nucleus compared with that of pyridine and a value of the total rate ratio greater than unity. In the case of 3-ethylpyridine, the activation is insufficient to overcome the normal deactivation of the position *para* to the alkyl group.

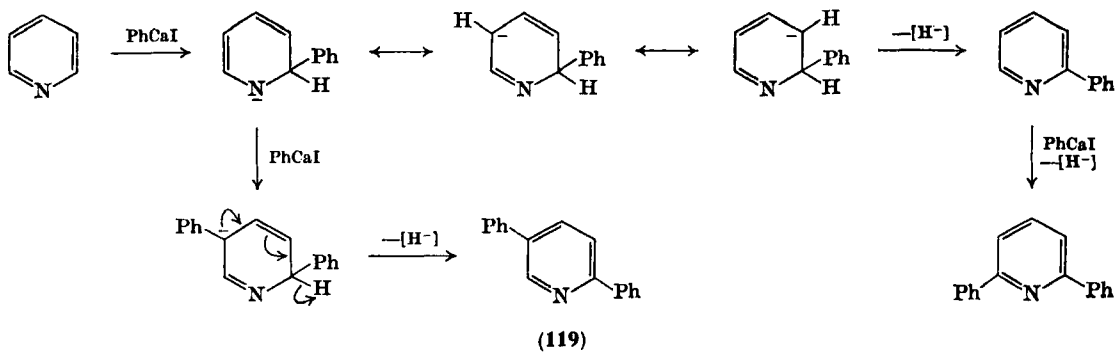
²⁵⁷ T. V. Talalaeva and K. A. Kocheshkov, *Dokl. Akad. Nauk SSSR* **104**, 260 (1955); *Chem. Abstr.* **50**, 5446 (1956).

Of the foregoing possible explanations put forward to account for the preferential formation of the 2,3-isomer in these reactions, only those can be retained which would explain the specific *activation* of C-2 by the alkyl substituent, although it is conceivable and even likely that a combination of factors is involved which favors the formation of more 2,3- than 2,5-isomer, but only one factor of which causes the observed activation. Steric acceleration, resulting from a relief of steric compression of the C-2 proton as the phenyl anion attacks almost perpendicularly to the plane of the ring, is ruled out by the fact that $^{\text{CH}_3}\text{F}_2 > ^{\text{Et}}\text{F}_2$. An attractive interaction of the nature of London dispersion forces is another possibility. As an ethyl substituent is expected to be more polarizable than a methyl, the former should have activated the 2-position more than the latter. Such an increased activation might, however, be more than counterbalanced by increasing steric hindrance to attack on going from a methyl to an ethyl group. Another novel explanation has been put forward which suggests that a loose complex, e.g., **118** (in which a monomeric phenyllithium has been assumed for simplicity until further information is available concerning its structure) might be formed between



the organolithium reagent and the methyl group of 3-picoline. The ring nitrogen atom is probably also complexed with lithium bromide (two molecules of base per molecule of LiBr) or with another molecule of phenyllithium. The attacking molecule would be favorably oriented for attack at C-2, and ΔH^\ddagger for the substitution would be sufficiently lowered to overcome the usual deactivation by the methyl group in nucleophilic aromatic substitutions. The lithium atom could be weakly bound to the methyl group by an electron-deficient bond of the type that has been postulated to explain the structures of tetrameric and hexameric ethyllithium both in solution and in the gas phase.²⁵⁸ A slight decrease in the stability of the electron-deficient bond on going from 3-picoline to the more branched 3-ethylpyridine

²⁵⁸ T. L. Brown, D. W. Diecherhoof, and D. A. Bafus, *J. Am. Chem. Soc.* **84**, 1371 (1962).



SCHEME V

would be expected either in terms of steric hindrance^{259, 260} or of the decreased electronegativity of the branched alkyl group.²⁶¹ On the basis of either an explanation for the activation based on London dispersion forces counterbalanced to a greater or lesser extent by steric hindrance, or on complexing through an electron-deficient type of bond, it was predicted that a 3-isopropyl group would give rise to an even smaller value of F_2 , probably less than unity. This has now been confirmed experimentally. The reaction of phenyllithium with mixtures of pyridine and 3-isopropylpyridine under competitive conditions has led to the following results²⁶²: ${}^{\text{iso-Pr}}K = 0.56$, ${}^{\text{iso-Pr}}F_2 = 0.82$, and ${}^{\text{iso-Pr}}F_6 = 0.30$. The corresponding values for nicotine are^{246a}: ${}^{\text{Nic}}K = 0.56$, ${}^{\text{Nic}}F_2 = 0.34$, and ${}^{\text{Nic}}F_6 = 0.79$. No competitive reactions have yet been carried out with other organolithium compounds and pyridines.

While it was suggested that the fact that the 2,3-:2,5-isomer ratio is less than one in the reaction of isopropyllithium with 3-picoline is due to steric hindrance arising from the increased bulk of the attacking reagent,²⁴⁵ it has also been found that when *o*-tolyllithium reacts with 3-picoline the 2,3-isomer comprises at least 96% of the total of mono-arylated products (some 4-arylated product may also have been formed in very low yield in this reaction).²⁶³ In the latter case, therefore, increasing the size of the attacking reagent also increases, if anything, the 2,3-:2,5-isomer ratio. These conflicting observations remain to be reconciled.

Phenylcalcium iodide and pyridine give 2-phenylpyridine and either 2,5- (119) or 2,6-diphenylpyridine, depending on conditions.²⁶⁴ Scheme V was tentatively proposed to account for the results. Phenylation of 2-phenylpyridine by phenylcalcium iodide gave only the 2,6-isomer. As was appreciated by the authors,²⁶⁴ the replacement of a hydride ion at C-5 by a phenyl anion is a controversial stage and seems, at first sight, mechanistically improbable. If the nitrogen atom is assumed to form a relatively stable complex with the calcium atom,

²⁵⁹ P. H. Lewis and R. E. Rundle, *J. Chem. Phys.* **21**, 986 (1953).

²⁶⁰ K. S. Pitzer and H. S. Gutowsky, *J. Am. Chem. Soc.* **68**, 2204 (1946).

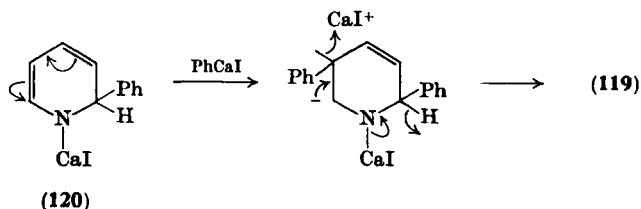
²⁶¹ G. E. Coates and F. Glockling, *J. Chem. Soc.* **1954**, 22.

²⁶² R. A. Abramovitch, C. S. Giam, and G. A. Poulton, Unpublished results (1964).

²⁶³ R. A. Abramovitch, C. S. Giam, and W. A. Hymers, Unpublished results (1964).

²⁶⁴ D. Bryce-Smith and A. C. Skinner, *J. Chem. Soc.* **1963**, 577.

then a more likely process (**120**→**119**) can be visualized, attack at C-3 being sterically hindered. Clearly, further work is needed on this very interesting experimental observation.



The Tschitschibabin reaction^{265, 266} of alkali metal amides with pyridine bases has been the subject of much recent discussion. While there is yet no agreement concerning the detailed mechanism (due to the lack of experimental information) there is no doubt that the overall reaction proceeds by an S_N2 type addition-elimination pathway.

Amination of pyridine with sodium or potassium amide proceeds at an appreciably higher temperature than the reaction with organolithium compounds (the addition step of which is exothermic at room temperature). Addition takes place at the α -positions in the first instance, and only when these are substituted, and at higher temperatures, are any 4-aminopyridine derivatives formed. Thus, in dimethylaniline at 110° , pyridine and sodamide give 2-aminopyridine in good yield.²⁶⁷ At that temperature, neither in dimethylaniline nor in toluene solution is any 4-aminopyridine formed in sufficient quantity to be detected by gas chromatography,²⁶⁸ although Tschitschibabin and Seide²⁶⁵ reported that small amounts of 4-amino- and 2,6-diaminopyridine were formed at 100 – 125° . At 170° , in the presence of a twofold excess of sodamide, 2,6-diaminopyridine is obtained, whereas with a large excess of sodamide at 200° in the absence of a solvent, 2,4,6-triaminopyridine is formed in poor yield.²⁶⁷ 2,6-Dimethylpyridine reacts with sodamide in toluene suspension at 110° to give 4-amino-2,6-dimethylpyridine.^{66, 269} When pyridine is heated

²⁶⁵ A. E. Tschitschibabin and O. A. Seide, *J. Russ. Phys. Chem. Soc.* **46**, 1216 (1914); *Chem. Abstr.* **9**, 1901 (1915).

²⁶⁶ M. T. Leffler, *Org. Reactions* **1**, 91 (1942).

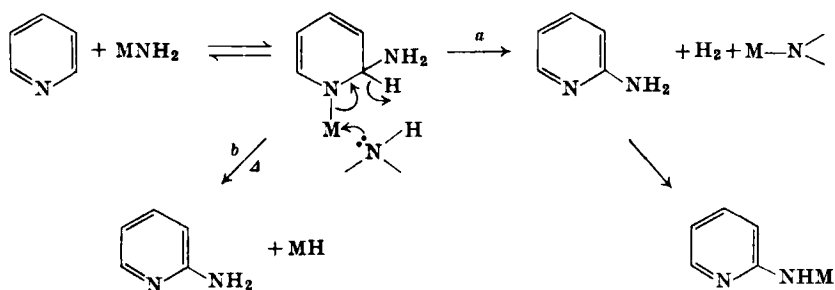
²⁶⁷ F. W. Bergstrom and W. C. Fernelius, *Chem. Rev.* **12**, 43 (1933).

²⁶⁸ R. A. Abramovitch, F. Helmer, and J. G. Saha, *Can. J. Chem.* **43**, 725 (1965).

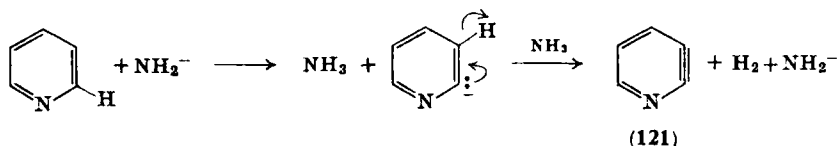
²⁶⁹ A. E. Tschitschibabin, *J. Russ. Phys. Chem. Soc.* **47**, 835 (1915).

at 80–130° with sodium in toluene in the presence of ammonia, a mixture of 2-amino- and 4-aminopyridine is said to be formed together with some 4,4'-dipyridyl.²⁷⁰

The mechanism proposed for the amination (path *a*), which accounts for the evolution of hydrogen, is illustrated in Scheme VI.¹ An alternative, and probably competing, pathway is the thermal decomposition mode *b*, which would be rendered more facile (as is observed)



by the presence of oxidizing agents such as potassium nitrate. On the other hand, it has recently been suggested that an elimination-addition mechanism was operating in this reaction which then involved the formation of a 2,3-pyridyne (121) (or, in some cases, of a 3,4-pyridyne).²⁷¹ Although a few examples of such reactions can be



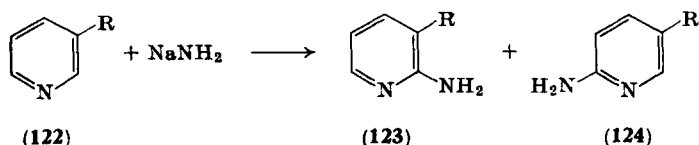
accounted for by such a mechanism—e.g., the reaction of 3-bromopyridine with sodium amide in liquid ammonia in the presence of acetophenone seems to be a well-authenticated example of a reaction proceeding *via* a pyridyne intermediate²⁷² (see Section IV, B)—there is a large body of evidence which runs contrary to this proposal, which

²⁷⁰ E. Schering, German Patent 358,397; *Chem. Abstr.* **17**, 2118 (1923).

²⁷¹ L. S. Levitt and B. W. Levitt, *Chem. Ind. (London)* **1963**, 1621.

²⁷² R. Levine and W. W. Leake, *Science* **121**, 780 (1955).

has been attacked from a number of quarters.²⁷³⁻²⁷⁶ In the first place, had a 2,3-pyridyne intermediate been involved one would have expected addition of a nucleophile to give mainly a 3-substituted pyridine, due to the electron-attracting character of the ring nitrogen atom.^{277, 278a,b} Second, as the results in Table VI indicate, an appreciable number of 3-substituted pyridines react with sodamide to give products in which the 2,3-isomer predominates, a result impossible on the basis of a pyridyne intermediate mechanism. Similarly, when an excess of a mixture of pyridine-3d and pyridine was heated with sodamide, the isotopic composition of the recovered unreacted pyridine-pyridine-3d mixture was the same as that of the starting material.²⁷⁴ When 3-picoline and sodamide were boiled in toluene and the products analyzed by gas chromatography, the 2,3-:2,5-isomer ratio was found to be 10.5:1. No 3,4-isomer was detected. This isomer ratio was unchanged within experimental error when 3-picoline-2d was used instead.²⁷⁴



Despite the foregoing evidence already present in the literature, Jones and Beveridge²⁹² have published molecular orbital calculations purporting to support the pyridyne intermediate mechanism, and have postulated "lone-pair interaction," which can result in the formation of a 2,3- or of a 2,6-pyridyne intermediate and explain the absence of any 3-aminopyridines among the reaction products. It was stated that lone-pair interaction would make a 2,3-pyridyne intermediate more

²⁷³ G. C. Barrett and K. Schofield, *Chem. Ind. (London)* **1963**, 1980.

²⁷⁴ R. A. Abramovitch, F. Helmer, and J. G. Saha, *Chem. Ind. (London)* **1964**, 659.

²⁷⁵ R. F. Childs and A. W. Johnson, *Chem. Ind. (London)* **1964**, 542.

²⁷⁶ Y. Ban and T. Wakamatsu, *Chem. Ind. (London)* **1964**, 710.

²⁷⁷ J. D. Roberts, D. A. Semenow, H. E. Simmons, Jr., and L. A. Carlsmith, *J. Am. Chem. Soc.* **78**, 601 (1956).

^{278a} J. D. Roberts, C. W. Vaughan, L. A. Carlsmith, and D. A. Semenow, *J. Am. Chem. Soc.* **78**, 611 (1956).

^{278b} G. B. R. de Graaff, H. J. den Hertog, and W. C. Melger, *Tetrahedron Letters* **1965**, 963.

TABLE VI
PRODUCTS OBTAINED IN THE REACTION OF 3-SUBSTITUTED
PYRIDINES (122) WITH SODAMIDE

| R in 122 | Products | Reference ^a |
|-------------------------------------|---|------------------------|
| CH ₃ | 2-Amino-3-picoline | 279 |
| CH ₃ | 2- and 6-Amino-3-picoline (123/124 = 10.5:1) | 274, 268 |
| C ₂ H ₅ | 2-Amino-3-ethylpyridine | 280 |
| C ₂ H ₅ | 2- and 6-Amino-3-ethylpyridine (123/124 = 3.5:1) (very crude quant. analysis) | 276 |
| n-C ₄ H ₉ | 2- and 6-Amino-3-n-butylpyridine (4:1) | 281 |
| NH ₂ | 2,3-Diaminopyridine | 282 |
| NHCH ₃ | 2-Amino-3-methylaminopyridine | 79 |
| CONH ₂ | 2-Aminonicotinamide | 89 |
| 2-N-Methylpyrrolidyl | 2- and 6-Aminonicotine | 283 |
| 2-N-Methylpyrrolyl | 2- (19%) and 6-Aminonicotyrine (26%) | 284, 285 |
| 2-Piperidyl | 2- and 6-Aminoanabasine | 286, 287 |
| 2-N-Methylpiperidyl | 2- and 6-Amino-N-methylanabasine | 287 |
| OH | 2,6-Diaminopyridine | 271, 288 |
| CO ₂ H | 2,6-Diaminopyridine | 289 |
| C≡CH | (2-Amino-3-ethynylpyridine)→7-azaindole | 291a |
| 3,4-Dihydroxy | 2-Amino-3,4-dihydroxypyridine | 290 |
| 5-Ethyl-2-methyl | 6-Amino-5-ethyl-2-methylpyridine | 275 |
| 2-Methyl-5-n-propyl | 6-Amino-2-methyl-5-n-propylpyridine | 275 |
| 5,6,7,8-Tetrahydro- isoquinoline | 1-Amino-5,6,7,8-tetrahydroiso- quinoline | 291 |
| 2,5-Dimethyl | 2-Amino-3,6-dimethylpyridine | 291b |

^a See footnotes.

²⁷⁹ O. Seide, *Ber.* **57**, 1802 (1924).

²⁸⁰ M. M. Robison and B. L. Robison, *J. Am. Chem. Soc.* **77**, 457 (1955).

²⁸¹ E. Hardegger and E. Nikles, *Helv. Chim. Acta* **39**, 505 (1956).

²⁸² A. Konopnicki and E. Plazek, *Ber.* **60**, 2045 (1927).

²⁸³ A. E. Tschitschibabin and A. W. Kirssanow, *Ber.* **57**, 1163 (1924).

²⁸⁴ G. R. Clemo and G. A. Swan, *J. Chem. Soc.* **1945**, 603.

²⁸⁵ A. W. Johnson, T. J. King, and J. R. Turner, *J. Chem. Soc.* **1960**, 1509.

²⁸⁶ M. I. Kabatchnik and M. M. Katznelsoln, *Bull. Soc. Chim. France* **2**, 576 (1935).

²⁸⁷ G. Menshikov, A. Grigorovich, and A. Orechov, *Ber.* **67**, 289 (1934).

²⁸⁸ E. Plazek, *Roczniki Chem.* **16**, 403 (1936).

²⁸⁹ H. Bojarska-Dahlig and P. Nantka-Namirski, *Roczniki Chem.* **30**, 612 (1956); *Chem. Abstr.* **51**, 4370 (1957).

²⁹⁰ I. S. Belonosov, *Zh. Prikl. Khim.* **22**, 1103 (1949); *Chem. Abstr.* **45**, 5650 (1951).

²⁹¹ R. Grewe, A. Mondon, and E. Nolte, *Ann.* **564**, 161 (1949).

^{291a} J. Reisch, *Ber.* **97**, 2717 (1964).

^{291b} A. Albert and R. E. Willette, *J. Chem. Soc.* **1964**, 4063.

²⁹² H. L. Jones and D. L. Beveridge, *Tetrahedron Letters* **1964**, 1577.

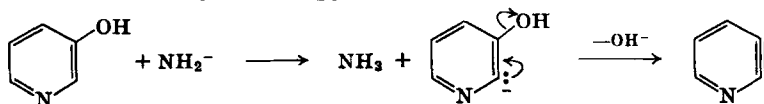
stable than a 3,4-pyridyne. It is remarkable, therefore, that in *none* of the reactions of 3-halopyridynes with potassium amide in liquid ammonia was any evidence forthcoming for the formation of a 2,3-pyridyne: only 3,4-pyridynes were generated (see Section IV, B). On the basis of a pyridyne intermediate mechanism in which the hydride ion elimination step is rate-determining, one would expect a deuterium isotope effect in the reaction of pyridine-3*d* with sodamide: this was not observed.²⁷⁴ If, on the other hand, it is the first, proton-abstraction step which is rate-determining, a change in the isomer ratio should have taken place when 3-picoline-2*d* was used instead of 3-picoline in the reaction with sodamide—again, such was not the case.²⁷⁴ Similarly, the amination of a mixture of pyridine-pyridine-2*d* established the absence of a primary kinetic deuterium isotope effect.²⁶⁸ These observations are contrary not only to the 2,3-pyridyne, but also to the 2,6-pyridyne concept, both of which are ruled out by the observation that 5-ethyl-2-methyl- and 2-methyl-5-*n*-propylpyridine are aminated at C-6.²⁷⁵ The absence of a deuterium isotope effect also eliminates a "1,2-pyridyne"-type intermediate (124a) from consideration, as do the substitutions on pyridines bearing β -substituents.



(124a)

Pyridines bearing substituents at the 2- or 4-positions are similarly aminated at the vacant α -position (see Table VII).

Two of the reactions summarized in Tables VI and VII require some comment. The reaction of 3-hydroxypyridine with an excess of sodamide at 210° results in the elimination of the hydroxyl group and the formation of 2,6-diaminopyridine. Plazek²⁸⁸ attributed this to the reduction of the phenolic function by nascent hydrogen. More recently, however, this reaction has been interpreted as providing evidence for the intermediacy of a 2,3-pyridyne species in this reaction²⁷¹:



Once again, if such were the case one would have expected to obtain some 3-aminopyridine which was not found. Also, 3,4-dihydroxypyridine is said to give 2-amino-3,4-dihydroxypyridine in the

TABLE VII
REACTION OF SODAMIDE WITH 2- OR 4-SUBSTITUTED PYRIDINES

| R = (in R—C ₅ H ₄ N) | Products | Reference ^a |
|--|--|------------------------|
| 2-CH ₃ | 6-Amino-2-picoline | 270 |
| 2-CH ₃ | 3,6-Diamino-2-picoline and 4,6-diamino-2-picoline | 293 |
| 4-CH ₃ | 2-Amino-4-picoline | 294 |
| 4-C ₂ H ₅ | 2-Amino-4-ethylpyridine | 97 |
| 4- <i>n</i> -C ₃ H ₇ | 2-Amino-4- <i>n</i> -propylpyridine | 295 |
| 4- <i>n</i> -Amyl | 2-Amino-4- <i>n</i> -amylpyridine | 296 |
| 4-Benzyl | 2-Amino-4-benzylpyridine | 296 |
| 2-OH | 6-Amino-2-pyridone | 297 |
| 4-OH | 2,6-Diamino-4-pyridone | 298 |
| 4-CO ₂ H | 2,6-Diaminopyridine | 289 |
| 4-CONH ₂ | 2,6-Diaminopyridine | 289 |
| 2-(2'-Pyridyl) | 6,6'-Diamino-2,2'-dipyridyl (?) | 299 |
| 4-(4'-Pyridyl) | 2,2'-Diamino-4,4'-dipyridyl | 300 |

^a See footnotes.

Tschitschibabin reaction,²⁹⁰ thus counteracting the example based on 3-hydroxypyridine. The second reaction to be discussed is that of 2-picoline with sodamide at a relatively high temperature, when 3,6-diamino-2-picoline (**126**) is one of the products isolated.²⁹³ If this is so, this represents another example of the type of orientation recently observed in the phenylation of pyridine with phenylcalcium iodide which gave some 2,5-diphenylpyridine.²⁶⁴ Alternatively, a 3,4-pyridyne intermediate (**125**) might perhaps actually be involved here. The evolution of hydrogen is not mentioned in this case. The decarboxylation of pyridine carboxylic acids under strongly basic conditions is unexceptional.

²⁹³ H. J. Schneiderwirth, U.S. Patent 2,068,353 (1937); *Chem. Abstr.* **31**, 1959 (1937).

²⁹⁴ O. Seide, *Ber.* **57**, 791 (1924).

²⁹⁵ W. Solomon, *J. Chem. Soc.* **1946**, 934.

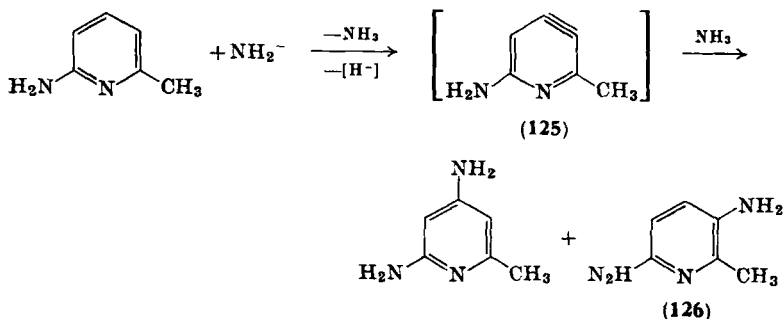
²⁹⁶ F. H. Case and W. A. Butte, *J. Org. Chem.* **26**, 4415 (1961).

²⁹⁷ A. E. Tschitschibabin, German Patent 374,291; *Chem. Abstr.* **18**, 2176 (1924).

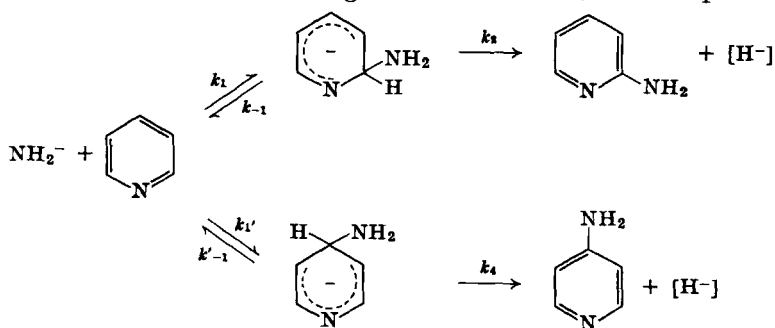
²⁹⁸ H. Bojarska-Dahlig and P. Nantka-Namirski, *Roczniki Chem.* **30**, 461 (1956); *Chem. Abstr.* **51**, 14722 (1957).

²⁹⁹ H. D. T. Willink, Jr., and J. P. Wibaut, *Rec. Trav. Chim.* **54**, 275 (1935).

³⁰⁰ Horsters and M. Dohrn, German Patent 398,204; *Chem. Zentr.* **95** (part II), 1409 (1924).



Molecular orbital calculations of the π -electron distribution in pyridine predict that more 4- than 2-aminopyridine should be formed in the Tschitschibabin reaction.^{4*} The fact that no 4-aminopyridine can be detected when the two positions are allowed to compete for a deficiency of sodamide (see, e.g., Abramovitch *et al*²⁶⁸) has led to the suggestion that the observed orientation in this reaction depends on the relative ease of elimination of a hydride ion from C-2 and C-4 and *not* upon the initial mode of addition (which, by implication, must take place predominantly at C-4 as predicted by the molecular orbital calculations).⁴ This hypothesis necessitates that the addition step be rapidly reversible and that the second stage, the elimination of hydride ion, be the rate-determining one (Scheme VII). Although it seems reasonable to assume that the hydride ion eliminations are the slow steps in this reaction, the fact that no deuterium isotope effect was observed in the reaction of 3-picoline-2*d* and of pyridine-2*d* with sodamide implies that the first stage must be virtually irreversible,²⁶⁸ as was found also in the case of the addition of phenyllithium to pyridine.²²⁹ The addition stage must, therefore, be the product-



SCHEME VII

*See, however, reference 8^b.

determining one. Unlike the situation found with 3-picoline and phenyllithium, however, competitive experiments have shown that in the Tschitschibabin reaction a 3-methyl group *does not* activate C-2 toward substitution as compared with the α -position in pyridine. The total rate ratio $\frac{^{\text{CH}_3}\text{H}}{\text{H}}K$ was found to be 0.22, while the partial rate factors were $^{\text{CH}_3}F_2 = 0.40$ and $^{\text{CH}_3}F_6 = 0.038$.²⁶⁸

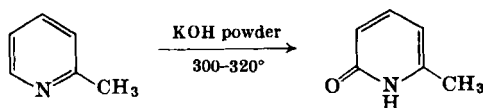
The question still remaining to be settled is that of the observed preferential attack at C-2 in the aminations of 3-substituted pyridines. This preferred orientation does not seem to depend on the electrical effect of the 3-substituent (see Table VII). Since an attempted kinetic study of the reaction has, until now, been thwarted by the insolubility of sodamide in the reaction medium,²⁶⁸ a somewhat related system was investigated,¹⁰ namely that involving the reaction between methoxide ion in methanol and 2-chloro-, 2-chloro-3-methyl-, and 2-chloro-5-methylpyridine. The very small and expected deactivating influence of the 3-methyl substituent and reactivity sequence 2-chloro > 2-chloro-3-methyl > 2-chloro-5-methyl were thus established as was the strong, if not dominating, influence of ΔS^\ddagger upon the reactivity, suggesting that solvation of the transition state may be very important. The slightly greater reactivity of 2-chloro-3-methylpyridine as compared with 2-chloro-5-methylpyridine might be due to *steric hindrance to solvation in the transition state leading to 2-methoxy-3-methylpyridine*. In the transition state, solvent molecules would tend to orient themselves around the attacking nucleophile and departing group and around the pyridine nitrogen atom: this stabilization of the transition state by solvation would lead to a decrease in ΔS^\ddagger and to a smaller increase (or even perhaps to a net decrease) in ΔH^\ddagger than would be expected from only the influence of the +I effect of the methyl group upon the ease of attack by a nucleophilic reagent. It is suggested that steric hindrance to solvation in the transition state may also account for the observed preferred attack at C-2 in those nucleophilic substitutions involving the displacement of a hydride ion. In the reaction of phenyllithium with 3-picoline, this effect could be reinforced by electron-deficient bonding or by London dispersion attractive forces between the attacking nucleophile and the methyl group to produce the observed activation of C-2.

A similar phenomenon might be contributing to the factors which determine the preferred attack at C-2 in, for example, the nitration of 3-ethoxy- and 3-carbethoxyaminopyridine (see Section III, A). Since the pyridine nitrogen is protonated in these cases, solvation of the

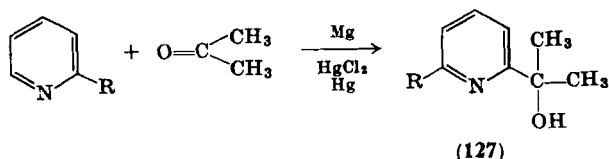
attacking nitronium ion, departing proton, and pyridinium cation would be required in the transition state, which would then probably require more solvation than the ground states.

The reaction of sodium alkylamides with pyridine gives 2-amino-pyridine derivatives,³⁰¹ but this does not appear to have been exploited with substituted pyridines. Similarly, pyridine gives 2-hydrazinopyridine on treatment with sodium hydrazide/hydrazine followed by hydrolysis.^{301a}

Hydroxylation of pyridine in unspecified yield has been effected by passing the vapors over potassium hydroxide powder at 300–320°. ³⁰² 2-Picoline is hydroxylated at C-6 in this way,³⁰³ and 3-hydroxypyridine gives 2,3-dihydroxypyridine.¹⁰²



The orientation of the entering nucleophile in the Emmert reaction^{304, 305} presents features which differ from those observed in the reactions of organolithium compounds with pyridines, and deserves further study. When pyridine is heated with acetone in the presence of magnesium and mercuric chloride, 2-pyridyldimethylcarbinol (**127**, R = H) is obtained. Unfortunately, the yields in this



and related reactions are rather low. 2-Picoline undergoes substitution at the 6-position (**127**, R = CH₃),³⁰⁴ but 3-picoline gives a mixture of the 2,3- and 2,5-isomers in undetermined proportions.^{304, 306} The

³⁰¹ K. Kovacs and T. Vajda, *Acta Chim. Acad. Sci. Hung.* **21**, 445 (1959); *Chem. Abstr.* **55**, 1608 (1961).

^{301a} T. Kauffmann, *Angew. Chem. Intern. Ed.* **3**, 342 (1964).

³⁰² A. E. Tschitschibabin, *Ber.* **56**, 1879 (1923).

³⁰³ A. E. Tschitschibabin, *Chem. Zentr.* **96** (part I), 1567 (1925).

³⁰⁴ B. Emmert and E. Asendorf, *Ber.* **72**, 1188 (1939).

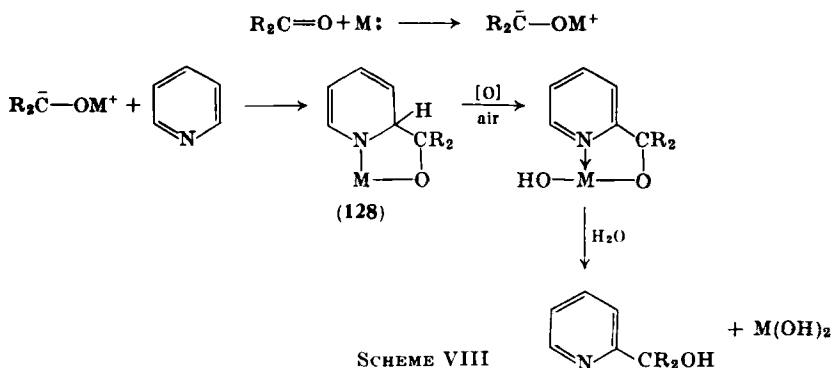
³⁰⁵ B. Emmert and E. Pirot, *Ber.* **74**, 714 (1941).

³⁰⁶ H. L. Lochte, P. F. Kruse, Jr., and E. N. Wheeler, *J. Am. Chem. Soc.* **75**, 4477 (1953).

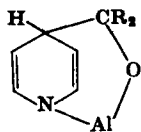


(128a)

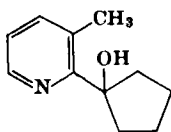
mechanism shown in Scheme VIII has been proposed for this reaction.³⁰⁷ The similarity between this reaction and the formation of pinacols from ketones had led to the alternative suggestion that the Emmert reaction involves the formation of radical intermediates of the type (128a).¹ The exact mechanism remains to be determined but a nucleophilic attack is assumed for the time being. If aluminum is used as the metal heterocatalyst, some 4-substitution products are



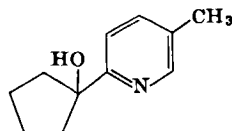
obtained³⁰⁶ and this has been explained³⁰⁷ by postulating the formation of a cyclic intermediate (129), the size of the aluminum atom (compared with magnesium) being such as to permit a transannular bridge between the nitrogen atom and the 4-position. Groups in the 2-position apparently interfere with the formation of the cyclic



(129)



(130)

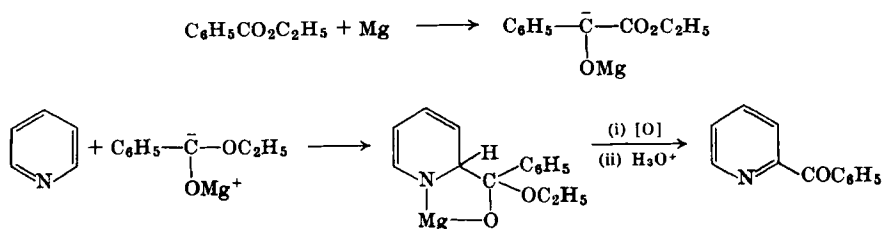


(131)

³⁰⁷ G. B. Bachman, M. Hamer, E. Dunning, and R. M. Schisla, *J. Org. Chem.* **22**, 1296 (1957).

coordination compound (128), since 2-picoline gives only a 2–15% yield of the 2,6-isomer and 2,6-lutidine gives no pyridyl alcohols. Relatively better yields are said to be obtained, however, with 3-picoline. Even there, however, the substituent may be exerting an appreciable steric effect. For example, 3-picoline and cyclopentanone gave a mixture consisting of 1-(3-methyl-2-pyridyl)-cyclopentanol (130) (4%) and 1-(5-methyl-2-pyridyl)cyclopentanol (131) (11%), i.e., the predominant product is that resulting from attack *para* to the methyl group. More quantitative work has now been carried out in our laboratory and some results are summarized here.^{307a} Reaction of pyridine with cyclohexanone and Mg gave only the 2-isomer (gas chromatography). In the presence of Al the 2-/4- isomer ratio was 79:21. 3-Picoline and cyclohexanone gave the 2- and the 6-substituted tertiary alcohols in the presence of magnesium, the isomer ratio was 71:29 in favor of the 3,6-disubstituted product. With 2-methylcyclohexanone, the 3,6-/2,3-isomer ratio was 75:25. If this reaction is a genuine nucleophilic substitution these results represent a reversal in the orientation usually observed in other nucleophilic substitution reactions of 3-picoline (except that with isopropyllithium).^{307a} Unfortunately, yields are rather low (15–20%) in these reactions. 4-Picoline reacts normally with various ketones to give the 2-pyridyl alcohol.^{306, 307} Some aromatic aldehydes and ketones have been used in the Emmert reaction.

A related reaction which leads to the direct introduction of an acyl group into the pyridine nucleus involves the reaction of benzoate esters or dimethyl amides with pyridine in the presence of magnesium or aluminum and mercury and mercuric chloride.³⁰⁸ When aluminum is used in the reaction of ethyl benzoate with pyridine, 2-benzoyl- (23.9%) and 4-benzoylpyridine (6.4%) are obtained. Under these



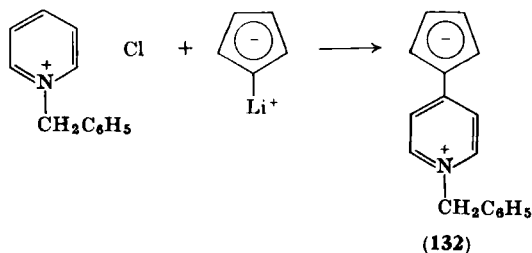
^{307a} R. A. Abramovitch and A. R. Vinutha, Unpublished results (1965).

³⁰⁸ G. B. Bachman and R. M. Schisla, *J. Org. Chem.* **22**, 1302 (1957).

conditions, *N,N*-dimethylbenzamide gives a 32% yield of the 2- and 6% yield of the 4-benzoyl derivatives. 4-Picoline and ethyl benzoate give 2-benzoyl-4-picoline (32.9%). The reaction and resulting orientation have not been studied with an unsymmetrically substituted pyridine derivative.

2. Pyridinium Salts

As expected, pyridinium salts are much more susceptible to nucleophilic attack than are the "free" bases, so that even relatively weak nucleophiles such as hydroxide ion and cyanide ion will attack the nucleus. In the presence of a suitable oxidizing agent to remove a hydride ion, the substitutions go to completion with the formation of an aromatic pyridinium salt. Powerful nucleophiles will, of course, add readily to pyridinium salts, but the resulting dihydropyridine intermediates are very prone to undergo polymerization in the presence of strong bases, and a lot of tars are formed in these reactions. For example, the reaction of phenyllithium with *N*-benzylpyridinium chloride gave a small amount of *N*-benzyl-1,2-dihydro-2-phenylpyridine (identified by reduction to the corresponding piperidine), but the main product consisted of a high-boiling polymeric tar.²⁴⁴ No pure addition product could be isolated from the reaction of *N*-benzyl-3-picolinium chloride and phenyllithium. An exception appears to be the reaction of *N*-benzylpyridinium chloride with cyclopentadienyllithium, which is reported to give the 4-cyclopentadienyl compound **132**.^{309, 310} This is undoubtedly due to the fact that the intermediate can aromatize readily to the internally stabilized zwitterionic compound. The fact that attack is taking place at C-4 instead of as usual

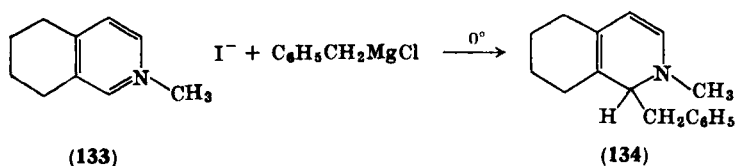


³⁰⁹ D. N. Kursanov and N. K. Baranetskaya, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk* 1703 (1961).

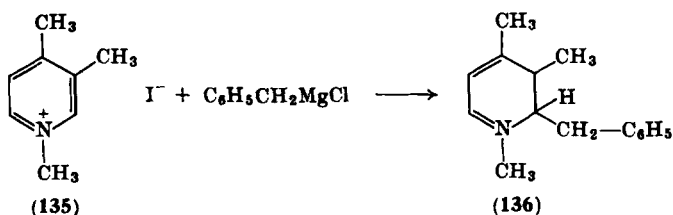
³¹⁰ D. N. Kursanov, N. K. Baranetskaya, and V. N. Setkina, *Dokl. Akad. Nauk SSSR* 113, 116 (1957).

at C-2 is probably related to the stability (and hence selectivity) of the cyclopentadienyl anion so that the transition state for the addition resembles the Wheland σ -complex.

Grignard reagents give readily isolable (though unstable) products with quaternary pyridinium salts. These have usually been reduced further instead of being oxidized to the fully aromatic level. For example, 5,6,7,8-tetrahydroisoquinoline methiodide (**133**) in ether suspension gives an 83% yield of 1-benzyl-1,2,5,6,7,8-hexahydro-*N*-methylisoquinoline (**134**) on being treated with benzylmagnesium chloride at 0°. ³¹¹ If the α -positions are blocked, attack takes place at



the γ -position, e.g., with acridine methiodide. ³¹² When the pyridinium salt bears a 3-substituent attack at C-2 is preferred to attack at C-6. Other examples of this general rule have been found by May and his co-workers. For example, 3,4-lutidine methiodide (**135**) and benzylmagnesium chloride give **136**. ²⁶³ *p*-Methoxybenzylmagnesium chloride reacts similarly. ^{313, 314} The same orientation was observed when the



reaction was carried out with 3,4-diethylpyridinium salts. ³¹⁵ 4-Picoline methiodide and benzylmagnesium chloride give a good yield of the unstable 1,2-dihydro derivative. ³¹⁶ These examples show that

³¹¹ R. Grewe and A. Mondon, *Ber.* **81**, 279 (1948).

³¹² M. Freund and G. Bode, *Ber.* **42**, 1746 (1909).

³¹³ E. L. May and J. H. Ager, *J. Org. Chem.* **24**, 1432 (1959).

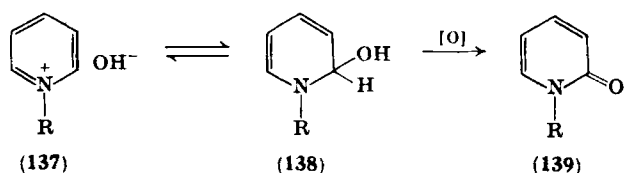
³¹⁴ J. H. Ager and E. L. May, *J. Org. Chem.* **25**, 984 (1960).

³¹⁵ J. H. Ager and E. L. May, *J. Org. Chem.* **27**, 245 (1962).

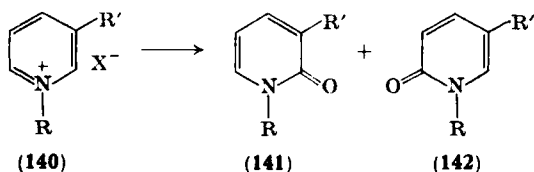
³¹⁶ N. B. Eddy, J. G. Murphy, and E. L. May, *J. Org. Chem.* **22**, 1370 (1957).

coordination of the Grignard reagent at the pyridine nitrogen atom is not necessary for substitution to take place, and that preferential attack at C-2 in a pyridine substituted at the 3-position does not require a cyclic transition state.

In alkaline solution, pyridinium salts are present as the quaternary hydroxides. The fact that such solutions did not obey Beer's Law led to the realization that the hydroxide (137) was in equilibrium with a



small amount of the pseudo-base **138**. If any oxidizing agent is present, **138** gives the pyridone **139**. The most common method of effecting pyridone formation by such a sequence involves the reaction of pyridinium salts with an alkaline ferricyanide solution. 2-Picoline methosulfate does not undergo this reaction, anhydro-base formation taking precedence.³¹⁷ The nature of the products obtained with a variety of 3-substituted pyridinium salts is summarized in Table IX. It should be emphasized that no quantitative analytical work has been carried out to determine the isomer ratios in those cases where a mixture of products is obtained. The results should be put on a more quantitative footing before any serious attempt is made at unravelling the orienting effects of the substituents. No product of attack at C-4 has ever been reported.

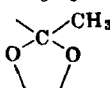


In most cases, 4-substituted pyridines react normally to give high yields of 2-pyridones. Esters of isonicotinic acid methiodide behave in this way.³²⁵ Isonicotinic acid methiodide itself, however, is said not to

³¹⁷ F. Bohlmann, N. Ottawa, and R. Keller, *Ann.* **587**, 162 (1954).

TABLE VIII

PYRIDONE FORMATION BY ALKALINE FERRICYANIDE OXIDATION OF
3-SUBSTITUTED PYRIDINIUM SALTS

| R in 140 | R' in 140 | X ⁻ | Product | Reference ^a |
|------------------------------------|--|--|---|------------------------|
| C ₂ H ₅ | CH ₃ | I ⁻ | 141 (24%) | 83 |
| CH ₃ | CH ₃ | CH ₃ SO ₄ ⁻ | 141 (41%) | 83 |
| CH ₃ | C ₂ H ₅ | CH ₃ SO ₄ ⁻ | 141/142 = 8:1 | 318 |
| CH ₃ | Br | I ⁻ | 141 (27%) (b.p. range) | 83 |
| CH ₃ | CN | I ⁻ | 141 and 142 (ratio not determined) | 83 |
| CH ₃ | CN | I ⁻ | 141 (main) + traces of 142 and 4-pyridone | 324a |
| CH ₃ | CONH ₂ | I ⁻ | 141 (15%) | 83 |
| CH ₃ | CONH ₂ | I ⁻ | 141 and 142 (about 1:1 ratio) | 319, 320 |
| CH ₃ | CO ₂ H | CH ₃ SO ₄ ⁻ | 142 | 83 |
| CH ₃ | C ₆ H ₅ | CH ₃ SO ₄ ⁻ | 142 | 321 |
| CH ₃ | CO ₂ C ₂ H ₅ | I ⁻ | 142 | 321 |
| CH ₃ | 3-Pyridyl | I ⁻ | 142 | 321 |
| CH ₃ | N-Methyl-pyrrolidyl | I ⁻ | 142 | 321 |
| CH ₂ CH ₂ Ph | N-Methyl-pyrrolidyl | Br ⁻ | 142 | 322 |
| CH ₂ CH ₂ Ph | OC ₆ H ₅ | Br ⁻ | 142 (30%) | 323 |
| CH ₃ |  | CH ₃ SO ₄ ⁻ | 142 | 324 |

^a See footnotes.

³¹⁸ S. Sugawara and M. Kirisawa, *Pharm. Bull. (Tokyo)* **4**, 139 (1956); *Chem. Abstr.* **51**, 6635 (1957).

³¹⁹ M. E. Pullman and S. P. Colowick, *J. Biol. Chem.* **206**, 121 (1954).

³²⁰ R. F. Dawson, D. R. Christman, A. D'Adamo, M. L. Solt, and A. P. Wolf, *J. Am. Chem. Soc.* **82**, 2628 (1960).

³²¹ S. Sugawara and M. Kirisawa, *Pharm. Bull. (Tokyo)* **3**, 187 (1955); *Chem. Abstr.* **50**, 8636 (1956).

³²² S. Sugawara and T. Tatsuno, *J. Pharm. Soc. Japan* **72**, 248 (1952).

³²³ H. Tomisawa, *Yakugaku Zasshi* **79**, 1173 (1959); *Chem. Abstr.* **54**, 3417 (1960).

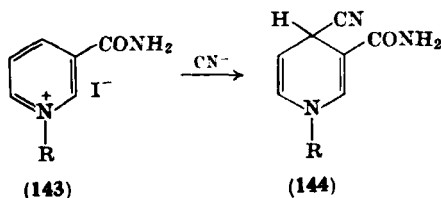
³²⁴ S. Sugawara and M. Kirisawa, *Pharm. Bull. (Tokyo)* **3**, 190 (1955); *Chem. Abstr.* **50**, 9415 (1956).

^{324a} T. Robinson and C. Cepurnek, *Phytochemistry* **4**, 75 (1965).

give a pyridone.³²⁵ Other 4-substituted derivatives also give the 2-pyridone (aldehyde and ketone functions must be protected to prevent their oxidation under the conditions of the reaction).^{326, 327}

The results in Table VIII are readily explainable in most cases if it is assumed that the rate- and product-determining step is the second or oxidation step, in which the equivalent of a hydride ion is eliminated, provided the first stage is rapidly reversible, which it has been shown to be. The combined electrical and steric effects of a 3-substituent upon the elimination and ease of approach by the reagent would have to be taken into consideration. Electron-donating substituents are expected to facilitate hydride-ion elimination more from the 2- than from the 6-position, whereas electron-attracting ones (e.g., CO₂H, 3-pyridyl, and CN) should have the opposite effect. The large *N*-methylpyrrolidyl group in the nicotine quaternary salt might well sterically hinder the formation of the 2-pyridone (perhaps by hindering the approach of the oxidizing agent). Some features of the results in Table VIII are not so readily explained and careful quantitative analysis of the reaction products as well as a determination of the effects of substituents upon reactivity seems to be very desirable. The presence of 4-pyridone derivatives, if any are formed, should be detectable by gas chromatography.

Cyanide ions attack the 4-position in pyridinium salts. For example, nicotinamide *pyr-N*-methiodide (143, R = CH₃) and diphosphopyridine nucleotide give the 4-cyano-1,4-dihydro derivatives (144).^{328, 329} 3-Acetyl-*N*-benzylpyridinium chloride similarly gives the 4-cyano-1,4-dihydro derivative and no attack at C-2 has been reported.³³⁰ Hydrosulfite reduction of nicotinamide quaternary salts



³²⁵ M. H. Fronk and H. S. Mosher, *J. Org. Chem.* **24**, 196 (1959).

³²⁶ S. Sugawara and M. Kirisawa, *Chem. Pharm. Bull. (Tokyo)* **6**, 615 (1958); *Chem. Abstr.* **54**, 14243 (1960).

³²⁷ H. Tomisawa, *Yakugaku Zasshi* **79**, 1167 (1959); *Chem. Abstr.* **54**, 3416 (1960).

³²⁸ M. Marti, M. Viscontini, and P. Karrer, *Helv. Chim. Acta* **39**, 1451 (1956).

³²⁹ A. San Pietro, *J. Biol. Chem.* **217**, 579 (1955).

³³⁰ A. G. Anderson, Jr., and G. Berkelhammer, *J. Org. Chem.* **23**, 1109 (1958).

also gives the 1,4-dihydro derivatives.^{331, 332} It has been suggested^{331, 333} that those reagents which readily form charge-transfer complexes with pyridinium salts attack at the 4-position; others substitute at the 2-position. The importance of charge-transfer complexes in determining eventual orientation in aromatic substitution is still a matter which is being debated although, as has been pointed out in the case of the dithionite reduction of diphosphopyridine nucleotide,³³¹ a suitably oriented charge-transfer complex would possess the right geometry for exclusive attack at C-4.

Most of the foregoing reactions really comprise only the first stage—the addition step—of what potentially is a nucleophilic substitution reaction. Under this heading, then, might also be included the reduction of pyridinium ions with sodium borohydride. With 3-substituted pyridines the 1,6-dihydro derivatives are apparently the main ones formed.³³⁴ (See also the article by Anderson and Lyle in this volume.)

3. Pyridine *N*-Oxides

Again, as expected, pyridine *N*-oxides are very susceptible to nucleophilic attack. Unlike the situation usually prevalent with the quaternary pyridinium salts, the elimination stage of the two-step nucleophilic substitution can occur with relative ease, the oxide grouping serving as a good sink for the leaving hydride ion electron-pair and being itself eliminated in the process. Considerably more work has been carried out on quinoline and isoquinoline *N*-oxides than on pyridine *N*-oxide derivatives.

Grignard reagents were said to give low yields of products with the *N*-oxides themselves. For example, phenylmagnesium bromide and pyridine *N*-oxide yielded a small amount of 2-phenylpyridine.^{335–337} Poor yields were also reported with *sec*-butyl and *n*-butylmagnesium bromides.³³⁸ It has recently been reported, however, that pyridine

³³¹ E. K. Kosower and S. W. Bauer, *J. Am. Chem. Soc.* **82**, 2191 (1960).

³³² K. Wallenfels and H. Schüly, *Ann.* **621**, 178 (1959).

³³³ E. K. Kosower, *J. Am. Chem. Soc.* **78**, 3497 (1956).

³³⁴ R. E. Lyle, D. A. Nelson, and P. S. Anderson, *Tetrahedron Letters* **1962**, 553.

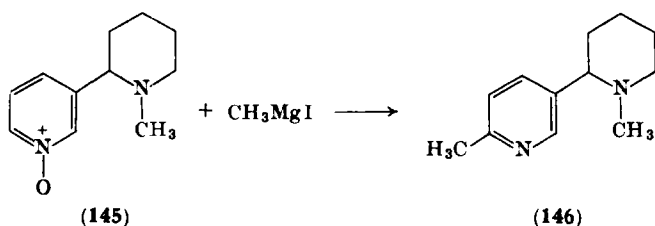
³³⁵ M. Colonna, *Boll. Sci. Fac. Chim. Ind. Bologna* **4**, 134 (1940); *Chem. Abstr.* **34**, 7290 (1940).

³³⁶ M. Colonna and A. Risaliti, *Gazz. Chim. Ital.* **83**, 58 (1953).

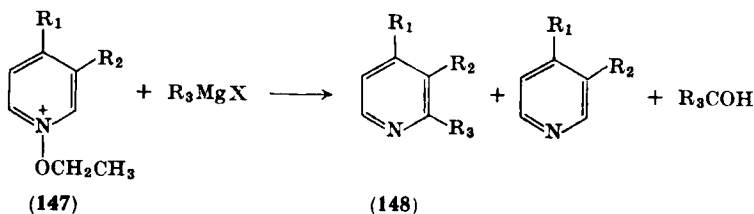
³³⁷ E. Ochiai and K. Arima, *J. Pharm. Soc. Japan* **69**, 51 (1949); *Chem. Abstr.* **44**, 1502 (1950).

³³⁸ Lowman, Ph.D. Dissertation, Columbia University (1948), quoted by R. C. Elderfield (see reference 340).

N-oxide and phenylmagnesium bromide in tetrahydrofuran give a good yield of 1-hydroxy-2-phenyl-1,2-dihydropyridine, which is easily dehydrated to 2-phenylpyridine.^{338a} Phenyllithium reacts very readily with pyridine *N*-oxide in ether suspension to give a number of products: one of these is 2-phenylpyridine but the others have not been identified yet.²⁶² In contrast to this, both *N*-methylanabasine *N'*-oxide (**145**) and the *N,N'*-dioxide react cleanly with methylmagnesium iodide to give 6-methyl-3-(*N*-methyl-2'-piperidyl)pyridine (**146**) (in 32% yield from **145**).³³⁹ The orientation is probably a reflection of the steric influence of the 3-substituent.



Pyridine *N*-oxide quaternary salts undergo substitution smoothly with Grignard reagents. *N*-Benzoyloxypyridinium chloride and a large excess of phenylmagnesium bromide give 2-phenylpyridine together with a diphenylpyridine.³⁴⁰ *N*-Ethoxypyridinium bromide salts (**147**) bearing substituents at the 3-position react with methyl, ethyl, and *n*-propyl Grignard reagents: the alkyl group of the Grignard reagent enters the 2-position of the pyridine nucleus and the ethoxyl group is eliminated. Partial decomposition of the quaternary salt to the tertiary base and dialkyl carbinol (via acetaldehyde) accompanies the formation of **148**.²⁰ Here again, as in the cases of other quaternary



^{338a} T. Kato and H. Yamanaka, *J. Org. Chem.* **3**, 910 (1965).

³³⁹ O. S. Otroschenko, A. S. Sadykov, M. U. Utebaev, and A. I. Isametova, *Zh. Obshch. Khim.* **33**, 1038 (1963).

³⁴⁰ R. C. Elderfield, "Heterocyclic Compounds," Vol. 4, p. 244. Wiley, New York, 1952.

pyridinium salts in which coordination of the Grignard reagent at nitrogen before substitution is not possible, it is the *ortho* position between the 3-substituent and ring nitrogen atom that is attacked preferentially.

As has already been mentioned, halogenation of the *N*-oxides with phosphorus pentachloride, phosphorus oxychloride, or sulfuryl chloride involves nucleophilic attack by halide ion upon the substrate complexed at the oxygen atom (with the last reagent, a complex $C_5H_5N^+-OSO_2Cl Cl^-$ is probably formed first). In the absence of the oxide group no ring chlorination occurs with phosphorus pentachloride or oxychloride.³⁴¹ The effects of substituents upon the orientation of the entering halogen atom are seen from the results given in Table IX which also lists the reagents and products obtained.

TABLE IX

CHLORINATION OF PYRIDINE *N*-OXIDES WITH PCl_5 , $POCl_3$, OR SO_2Cl_2

| Substituents | Reagent and conditions | Products | Reference ^a |
|---------------------|--|---|------------------------|
| None | SO_2Cl_2 | 2-Chloropyridine (main) 4-Chloropyridine (minor) | 188 |
| None | PCl_5 , 140° | 4-Chloropyridine | 187 |
| 2-CH ₃ | $POCl_3$, 140–150° | 4-Chloro-2-picoline (60%) 6-Chloro-2-picoline 2-Picolyl chloride (8%) | 342 |
| 2,6-Dimethyl | $POCl_3$, 140–150°, 3 hours | 4-Chloro-2,6-lutidine (60–70%) 6-Methyl-2-picolyl chloride (1–2%) | 343 |
| 3-Bromo | SO_2Cl_2 , 110–120°, 2 hours | 3-Bromo-4-chloropyridine (main) 3-Bromo-2-chloropyridine 3-Bromo-6-chloropyridine (least) | 344 |
| 3-CONH ₂ | $POCl_3$, PCl_5 , 115–120°, 1.5 hours | 2-Chloro-3-cyanopyridine (52%) No 6-chloro derivative | 345 |

³⁴¹ E. C. Taylor, Jr., A. J. Crovetti, and H. M. Loux, *J. Am. Chem. Soc.* **77**, 5445 (1955).

³⁴² E. Ochiai, M. Fujimato, and S. Ichimura, *Pharm. Bull. (Tokyo)* **2**, 137 (1954); *Chem. Abstr.* **50**, 991 (1956).

³⁴³ T. Kato and M. Ohta, *J. Pharm. Soc. Japan* **71**, 217 (1951); *Chem. Abstr.* **46**, 4541 (1952).

³⁴⁴ H. J. den Hertog and N. A. I. M. Boelrijk, *Rec. Trav. Chim.* **70**, 578 (1951).

TABLE IX—*cont.*

| Substituents | Reagent and conditions | Products | Reference ^a |
|---|--|--|------------------------|
| 3-CO ₂ H | POCl ₃ , PCl ₅ , 115–120°, 1.5 hours; then H ₂ O | 2-Chloronicotinic acid (41%) 4-Chloronicotinic acid (5%) No 6-Chloro derivative | 345 |
| 3-NO ₂ | POCl ₃ | 2-Chloro-3-nitropyridine (30%) 6-Chloro-3-nitropyridine (8.4%) | 346 |
| 3-CONH ₂ - 4-OCH ₃ | PCl ₅ , POCl ₃ , 115–120°, 1.5 hours | 2,4-Dichloronicotinonitrile (33%) | 347 |
| 3,5-Dibromo | SO ₂ Cl ₂ , 110–120°, 2 hours | 2-Chloro-3,5-dibromopyridine (60%) 4-Chloro-3,5-dibromopyridine (40%) | 348 |
| 3,5-Diethoxy | SO ₂ Cl ₂ , 0°, 24 hours | 2,6-Dichloro-3,5-diethoxy-pyridine (15–20%) 3,5-Diethoxy-2,4,6-trichloro-pyridine (5–10%) | 348 |
| 3,4-Dichloro | SO ₂ Cl ₂ , 90–100° | 2,3,4-Trichloropyridine (main) 3,4-Dichloro-2-pyridone (small amount) 2,4,5-Trichloropyridine (suspected presence) | 157 |
| 4-OH | SO ₂ Cl ₂ , 140°, 4 hours | 1,2,2,3,3,5,6-Heptachloro-1,2,3,4-tetrahydro-4-pyridone | 157 |
| 4-NO ₂ | SO ₂ Cl ₂ , 110°, 6 hours | 2,4-Dichloropyridine (35–40%) 2,3,4,5-Tetrachloropyridine | 154 |
| 4-CONH ₂ | PCl ₅ , POCl ₃ , 120–130°, 5 hours | 2-Chloro-4-cyanopyridine | 349 |

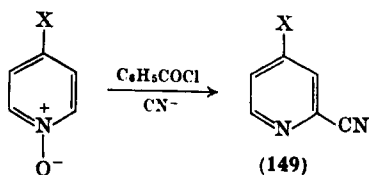
^a See footnotes.

Apart from the bromine atom, the other 3-substituents again direct mainly to the 2-position. The possibility of a cyclic transition state being involved at least in part in the reactions with phosphorus

³⁴⁵ E. C. Taylor, Jr., and A. J. Crovetti, *J. Org. Chem.* **19**, 1633 (1954).³⁴⁶ E. C. Taylor, Jr., and J. S. Driscoll, *J. Org. Chem.* **25**, 1716 (1960).³⁴⁷ E. C. Taylor, Jr., and A. J. Crovetti, *J. Am. Chem. Soc.* **78**, 214 (1956).³⁴⁸ H. J. den Hertog and C. Hoogzand, *Rec. Trav. Chim.* **76**, 261 (1957).³⁴⁹ Y. Suzuki, *Yakugaku Zasshi* **81**, 1204 (1961); *Chem. Abstr.* **56**, 3445 (1962).

pentachloride and phosphorus oxychloride has been mentioned already.

Cyanide ion does not react with pyridine *N*-oxide nor does this substance undergo the Reissert reaction. 4-Halopyridine *N*-oxides are exceptional in reacting with cyanide ion in the presence of benzoyl chloride, giving the 2-cyano-4-halopyridines (**149**).³⁵⁰ In contrast to this, *N*-alkoxy-quaternary salts of pyridine have been found to yield



the corresponding cyano-substituted heterocycles under very mild conditions (potassium cyanide in aqueous solution).^{21-23, 351, 352} Table X summarizes the results of the substitution by cyanide anion of hydride ions in *O*-alkylated pyridine *N*-oxides. The minor differences between the results of various authors that appear in Table X are probably due to the fact that in some cases the reactions were carried out in aqueous solution while in others aqueous dioxan was used. Although at first sight the orientation with a 3-carbethoxyl group may appear to be discordant, it should be recalled that exclusive substitution at C-6 was observed when such a substituent was present in the alkaline ferricyanide oxidation of the corresponding *N*-methylpyridinium salt (Table VIII). The structures of the nitriles obtained in the reaction with the 3-carboxylic ester were confirmed (i) by their ultraviolet absorption spectra and (ii) by hydrolysis to the dicarboxylic acids followed by esterification to the known dicarboxylic methyl esters.³⁵² In general, apart from this one exception, the usual pattern is observed, in which 3-substituent will direct the entering nucleophile predominantly to C-2, whether it be electron-attracting or -donating. In this case, however, such a generalization should be tempered by caution since a number of external factors have been found to affect the isomer ratios quite drastically in some instances.³⁵² It should also be emphasized once again that quantitative analyses of isomer ratios and measurements of relative reactivities have not been carried out,

³⁵⁰ E. Ochiai and I. Nakayama, *Yakugaku Zasshi* **65B**, 582 (1945).

³⁵¹ T. Okamoto and H. Tani, *Chem. Pharm. Bull. (Tokyo)* **7**, 925 (1959).

³⁵² H. Tani, *Chem. Pharm. Bull. (Tokyo)* **7**, 930 (1959).

TABLE X
SUBSTITUTION OF *N*-METHOXPYRIDINIUM SALTS BY CYANIDE ION

| Substituents | Products |
|---|--|
| None ^a | 2-Cyanopyridine (48%), 4-cyanopyridine (24%) |
| None ^b | 2-Cyanopyridine (49%), 4-cyanopyridine (32%) |
| 2-CH ₃ ^a | 6-Cyano-2-picoline (45%), 4-cyano-2-picoline (18%) |
| 2-CH ₃ ^b | 6-Cyano-2-picoline (48%), 4-cyano-2-picoline (10%) |
| 3-CH ₃ ^a | 2-Cyano-3-picoline (30%), 4-cyano-3-picoline (15%) |
| 3-CH ₃ ^c | 2-Cyano-3-picoline (36%), 4-cyano-3-picoline (6%), 6-cyano-3-picoline (6%) |
| 4-CH ₃ ^{a, b} | 2-Cyano-4-picoline (30-40%) |
| 2,4-Dimethyl ^b | 6-Cyano-2,4-lutidine (73%) |
| 2,6-Dimethyl ^b | 4-Cyano-2,6-lutidine (40%) |
| 2,6-Dimethyl ^a | 4-Cyano-2,6-lutidine (33%), 6-cyanomethyl-2-picoline |
| 3-CN ^c | 2,3-Dicyanopyridine (28%), 2,5-dicyanopyridine (17.6%) |
| 4-CN ^b | 2,4-Dicyanopyridine (54%) |
| 3-CO ₂ C ₂ H ₅ ^{c, d} | Ethyl 4-cyanopyridine-3-carboxylate (31.6%), ethyl 6-cyanopyridine-3-carboxylate (19%) |
| 3-OCH ₃ ^c | 2-Cyano-3-methoxypyridine (68%) |
| 3,5-Dibromo ^c | 2-Cyano-3,5-dibromopyridine (70%) |

^a Okamoto and Tani.³⁵¹^c Tani.²¹^b Feely and Beavers.²³^d Tani.³⁵²

and that the above data, based as they are upon fractional crystallizations or distillations, *may* give a completely erroneous picture of the actual orienting influence of substituents. In the reaction of 1-methoxypyridinium iodide with potassium cyanide, low temperatures seem to favor the formation of 2-cyanopyridine, while higher temperatures (but below 60°) favor the production of 4-cyanopyridine (Table XI).

TABLE XI
EFFECT OF TEMPERATURE UPON THE RATIO OF 4- TO 2-CYANOPYRIDINE
PRODUCED IN THE REACTION OF 1-METHOXPYRIDINIUM IODIDE WITH
POTASSIUM CYANIDE IN AQUEOUS ETHANOL^a

| Temperature (°C): | 2 | 10 | 20 | 30 | 40 | 50 | 60 |
|---|------|------|------|------|------|------|------|
| Ratio of 4-cyanopyridine to 2-cyanopyridine | 0.06 | 0.11 | 0.23 | 0.69 | 1.43 | 2.01 | 2.03 |
| Over-all yield (%) | 80.2 | 91.1 | 89.1 | 94.1 | 89.1 | 83.2 | 69.3 |

^a From Tani.³⁵²

The effect of change of solvent is also quite marked, as seen from the data in Table XII.³⁵² An effect of pH upon the isomer ratio for the reaction with 1-methoxypyridinium iodide was also observed: as the pH of the initial reaction mixture was raised from 10.07 to 11.91, the 4-/2- isomer ratio fell from 1.67 to 0.49. Finally, the influence of an

TABLE XII

A: EFFECT OF SOLVENT UPON PRODUCT ISOMER RATIO IN REACTION OF 1-METHOXPYRIDINIUM IODIDE WITH POTASSIUM CYANIDE AT 10° FOR 30 MINUTES

| Solvent: | H ₂ O | H ₂ O—EtOH (1:1) | H ₂ O—EtOH (3:7) | H ₂ O—EtOH (2:8) | EtOH | Dioxan |
|---|------------------|--------------------------------|--------------------------------|--------------------------------|------|--------|
| Ratio of 4-cyano- pyridine to 2-cyano- pyridine | 0.45 | 0.26 | 0.17 | 0.11 | 0.08 | 0.11 |
| Over-all yield (%) | 34.7 | 69.3 | 86.1 | 91.1 | 83.2 | 88.1 |

B: EFFECT OF SOLVENT UPON PRODUCT ISOMER RATIO IN REACTION OF 1-METHOXY-3-CARBETHOXPYRIDINIUM METHOSULFATE WITH POTASSIUM CYANIDE AT 20° FOR 30 MINUTES

| Solvent: | H ₂ O | EtOH |
|---------------------------------|------------------|----------------------------|
| Ratio of 4- to 6-cyano compound | 1.66 | 0 (only 6-isomer isolated) |
| Over-all yield (%) | 63.3 | 62.7 |

internal factor was also investigated, namely the size of the *O*-alkylating group. The results in Table XIII indicate that the larger this group the greater the proportion of 4-isomer formed, and this has been interpreted in terms of steric inhibition of attack by the cyanide ion at the 2-position.³⁵² The relative ease of elimination of the alkoxy anions in the second stage of the reaction may well also be playing a role here. The above results have been taken to support a two-stage mechanism (the first step of which is, presumably, rapidly reversible) in which the decomposition of the intermediates to give products with the elimination of alkoxide anion (the alcohol has been isolated) is the

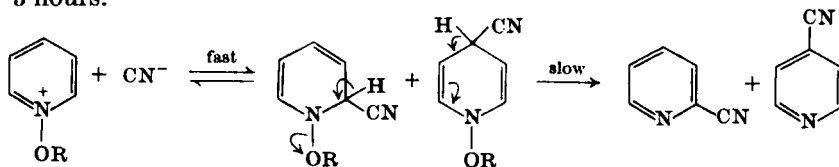
TABLE XIII

EFFECT OF *O*-ALKYL GROUP SIZE UPON ISOMER RATIO IN THE REACTION OF *N*-ALKOXYPYRIDINIUM SALTS WITH POTASSIUM CYANIDE IN AQUEOUS ETHANOL AT 20° FOR 30 MINUTES^a

| Salt: | 1-Methoxy- pyridinium iodide | 1-Ethoxy- pyridinium iodide | 1-Butoxy- pyridinium <i>p</i> -toluene- sulfonate |
|------------------------------------|------------------------------------|-----------------------------------|--|
| Over-all yield (%) | 89.1 | 78.8 | 72.8 |
| Ratio of 4- to 2- cyanopyridine | 0.23 | 2.84 | 2.17 |

^a From Tani.³⁵²

rate-determining and product-determining stage.^{23, 352} A deep yellow color (λ_{\max} 382 $m\mu$), thought to be associated with the dihydro-pyridine intermediate, was noted in the early stages of the reaction.^{23, 352} It was also felt that a charge transfer complex was not necessarily involved in the reaction since no iodopyridine was formed when an *N*-alkoxypyridinium iodide was heated in water at 100° for 3 hours.²³



When the adduct of pyridine *N*-oxide and *p*-toluenesulfonyl chloride is heated to about 205° one of the products formed is 3-tosyloxy pyridine.¹⁸⁷ The other products isolated are 2,3'-dipyridyl ether, *N*-(2'-pyridyl)-2-pyridone, *N*-(2'-pyridyl)-5-chloro-2-pyridone, and *N*-(2'-pyridyl)-3-chloro-2-pyridone.¹⁶¹ 3-Picoline gives, among other compounds, 5-tosyloxy-3-picoline.^{353, 354} Various mechanisms have been proposed for the formation of the 3-tosyloxy derivative.³⁵⁵⁻³⁵⁷

³⁵³ E. Matsumura, *J. Chem. Soc. Japan* **74**, 363 (1953); *Chem. Abstr.* **48**, 6442 (1954).

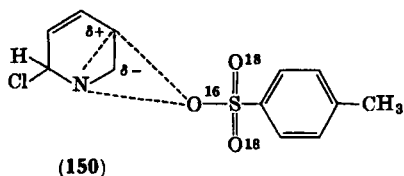
³⁵⁴ E. Matsumura, *J. Chem. Soc. Japan* **74**, 446 (1953); *Chem. Abstr.* **48**, 6442 (1954).

³⁵⁵ M. Murakami and E. Matsumura, *J. Chem. Soc. Japan* **68**, 88 (1949).

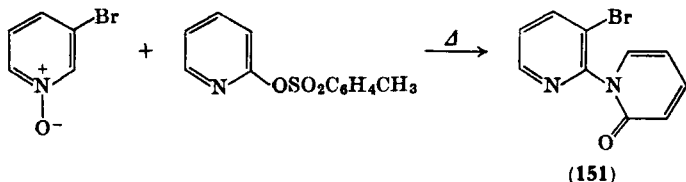
³⁵⁶ E. Ochiai and T. Yokokawa, *J. Pharm. Soc. Japan* **75**, 213 (1955); *Chem. Abstr.* **50**, 1819 (1956).

³⁵⁷ S. Oae, T. Kitao, and Y. Kitaoka, *Tetrahedron* **19**, 827 (1963).

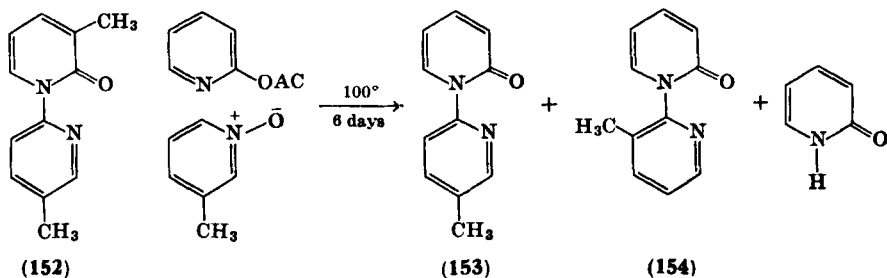
On the basis of studies using O^{18} , Oae and his co-workers³⁵⁷ modified the mechanism proposed by Ochiai and Yokokawa³⁵⁶ and suggested that the main path of this reaction proceeds via an intimate ion pair as depicted in **150**. The mechanism of the formation of the pyridyl-2-pyridones has not been clarified yet but a number of observations are



undoubtedly relevant. Thus, when 3-bromopyridine *N*-oxide is heated with 2-tosyloxypyridine, *N*-(3'-bromo-2'-pyridyl)-2-pyridone (**151**) is formed. Similarly, when 2-tosyloxypyridine and pyridine



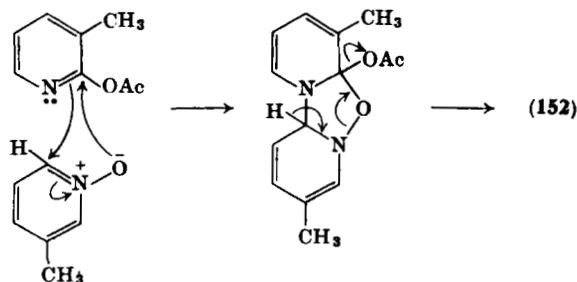
N-oxide are heated, *N*-(2'-pyridyl)-2-pyridone (30%), 2,3'-dipyridyl ether, and *N*-(4'-pyridyl)-2-pyridone are obtained.³⁵⁸ It was also observed that, when 3-picoline *N*-oxide was heated with acetic anhydride and then water, 3-methyl-*N*-(5'-methyl-2'-pyridyl)-2-pyridone (**152**) (4%) was isolated together with the expected 3- and 5-methyl-2-pyridones³⁵⁹ (see also Section V, B). When 3-picoline



³⁵⁸ P. A. de Villiers and H. J. den Hertog, *Rec. Trav. Chim.* **76**, 647 (1957).

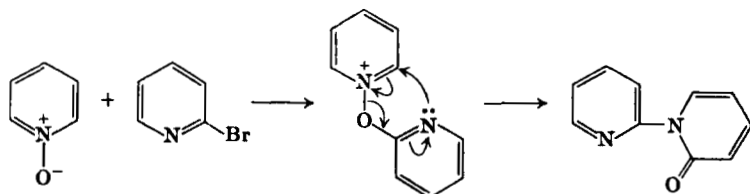
³⁵⁹ B. M. Bain and J. E. Saxton, *J. Chem. Soc.* **1961**, 5216.

1-oxide and 2-acetoxypyridine were heated at 100° for 6 days, a mixture of *N*-(5'-methyl-2'-pyridyl)-2-pyridone (**153**) (10%), *N*-(3'-methyl-2'-pyridyl)-2-pyridone (**154**) (4%), and 2-pyridone could be isolated. This resulted in the proposal of Scheme IX for the formation

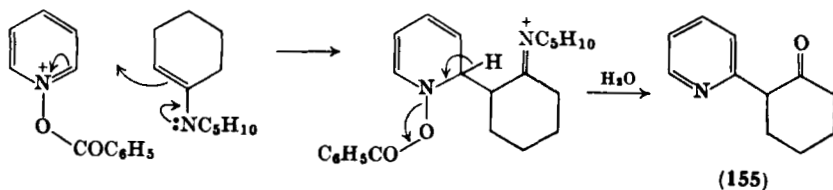


SCHEME IX

of **152**.³⁵⁹ The reaction of 2-bromopyridine and pyridine *N*-oxide very likely proceeds via an *O*-pyridyl salt which rearranges to *N*-(2'-pyridyl)-2-pyridone.¹⁵⁰

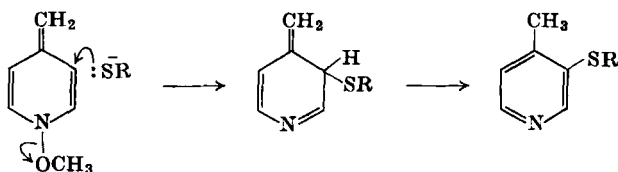


Two other nucleophilic substitution reactions of pyridine *N*-oxides deserve mention and further study to determine the effects of substituents. Pyridine *N*-oxide, benzoyl chloride, and the piperidine enamine of cyclohexanone give a good yield of 2-(2'-pyridyl)cyclohexanone (**155**) (63%).³⁶⁰ When *N*-methoxy-4-picolinium methyl



³⁶⁰ M. Hamana and H. Noda, *Chem. Pharm. Bull. (Tokyo)* **11**, 1331 (1963).

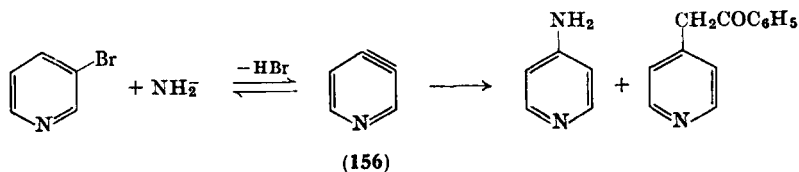
sulfate is treated with sodium *n*-propylmercaptide in excess 1-propanethiol (containing a little ethanol), a mixture consisting of 4-picoline, 2-*n*-propylmercapto-4-picoline, 3-*n*-propylmercapto-4-picoline, 4-[(propylmercapto)methyl]pyridine, and 1,2-di-(4-pyridyl)-ethane was obtained.³⁶¹ The formation of 3-*n*-propylmercapto-4-picoline may follow the course suggested for the mechanism of formation of 3-acetoxy-4-picoline in the reaction of 4-picoline *N*-oxide with acetic anhydride³⁶² (see Section V, B). This interesting work has recently been expanded further.^{362a}



B. ELIMINATION-ADDITION MECHANISM

This topic has been reviewed by den Hertog and van der Plas in Volume 4 of this series, and only a few words will be said about it here so as to round off the topic of nucleophilic substitution in the pyridine series.

4-Phenacylpyridine and 4-aminopyridine are formed in the reaction of 3-bromopyridine with sodioacetophenone and sodamide in liquid ammonia.²⁷² The 3,4-pyridyne intermediate (156) formed by elimination adds the nucleophiles present in solution. In view of the observations³⁶³⁻³⁶⁵ that when 3-halopyridines are treated with potassium



³⁶¹ L. Bauer and L. A. Gardella, *J. Org. Chem.* **28**, 1323 (1963).

³⁶² V. J. Traynelis and R. F. Martello, *J. Am. Chem. Soc.* **82**, 2744 (1960).

^{362a} L. Bauer and T. E. Dickerhofe, *J. Org. Chem.* **29**, 2183 (1964).

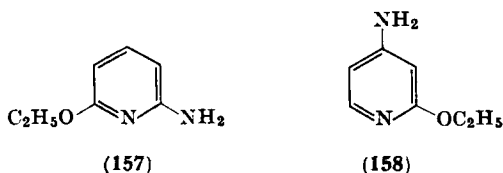
³⁶³ M. J. Pieterse and H. J. den Hertog, *Rec. Trav. Chim.* **80**, 1376 (1961).

³⁶⁴ M. J. Pieterse, Ph.D. Thesis, Amsterdam University (1962).

³⁶⁵ W. Czuba, *Rec. Trav. Chim.* **82**, 997 (1963).

amide in liquid ammonia the resulting 3,4-pyridyne gives a mixture of 3- and 4-aminopyridine, one might have expected the formation of some 3-aminopyridine as well in the above reaction.

When 3-chloro- or 3-bromopyridine is heated with lithium piperidide and piperidine in boiling ether, **156** is formed, which reacts further with piperidine to give a mixture of 3- and 4-piperidinopyridine in the ratio of 48:52. No 2,3-pyridyne intermediate is apparently produced under these conditions.³⁶⁶ Such an intermediate is probably involved in the reaction of potassium amide in liquid ammonia with 3-bromo-4-ethoxypyridine, which gives 2-amino-4-ethoxypyridine (55–60%). The reaction is, however, complicated by the fact that 2-amino-5-bromo-4-ethoxypyridine (15–20%) and 4-ethoxypyridine (25%) are also obtained.³⁶⁷ The formation of these two by-products may proceed by the preliminary disproportionation of some 3-bromo-4-ethoxypyridine to 3,5-dibromo-4-ethoxypyridine and 4-ethoxypyridine.³⁶⁸ The remarkable observation that both 2-amino-6-ethoxypyridine (**157**) (85%) and 4-amino-2-ethoxypyridine (**158**) (15%) are formed during the amination of 2-bromo-6-ethoxypyridine³⁶⁷ still requires explanation. No such rearrangement is observed with lithium piperidide.^{368a}



Whereas an elimination-addition mechanism is not involved in the reaction of pyridines with alkali-metal amides, the reaction of potassium amide with 2-chloropyridine *N*-oxide probably involves the intervention of 2,3-dehydropyridine *N*-oxide.^{368b} 3,4-Dehydropyridine *N*-oxide is an intermediate in the reaction of 3-chloropyridine *N*-oxide with piperidine.^{368c}

³⁶⁶ T. Kauffmann and F. Boettcher, *Ber.* **95**, 1528 (1962).

³⁶⁷ H. J. den Hertog, M. J. Pieterse, and D. J. Buurman, *Rec. Trav. Chim.* **82**, 1173 (1963).

³⁶⁸ M. J. Pieterse and H. J. den Hertog, *Rec. Trav. Chim.* **81**, 855 (1962).

^{368a} H. C. Van der Plas, T. Hijwegen, and H. J. den Hertog, *Rec. Trav. Chim.* **84**, 53 (1965).

^{368b} R. J. Martens and H. J. den Hertog, *Rec. Trav. Chim.* **83**, 621 (1964).

^{368c} T. Kauffmann and R. Wirthwein, *Angew. Chem.* **76**, 993 (1964).

V. Homolytic Substitution

A. PYRIDINES

The free radical substitution reactions, other than phenylation, of pyridine and its derivatives have received but scant attention. Alkylation of pyridine itself has been studied briefly, the alkyl radicals being generated either by the thermolysis of diacyl peroxides or of lead tetraacetate in acetic acid, or by electrolysis of the carboxylic acid precursor (for summary, see Norman and Radda³⁶⁹). Most of the available results are summarized in Table XIV. These figures on isomer ratios are not very reliable since the analyses were carried out by

TABLE XIV
FREE RADICAL ALKYLATION OF PYRIDINE^a

| Radical | Source | Over-all yield (%) | Ratio of 2- to 4-substi- tuted product |
|---|---|-----------------------|---|
| CH ₃ · | (CH ₃ COO) ₂ at 100° | 86 | 7.62 |
| CH ₃ · | Electrolysis of CH ₃ CO ₂ H | 3.5 | 2.81 |
| CH ₃ CH ₂ · | (CH ₃ CH ₂ COO) ₂ at 100° | 87 | 2.14 |
| CH ₃ CH ₂ · | Electrolysis of CH ₃ CH ₂ CO ₂ H | 6.8–14.3 | 1.25–2.78 |
| CH ₃ CH ₂ CH ₂ · | (CH ₃ CH ₂ CH ₂ COO) ₂ at 115° | 84 | 2.4 |
| CH ₃ CH ₂ CH ₂ · | Electrolysis of CH ₃ CH ₂ CH ₂ CO ₂ H | 4.38 | 5.07 |

^a From Goldschmidt and Minsinger.³⁷⁰

fractional distillation. In fact, it has now been established that an appreciable amount of 3-picoline is also formed in the thermal decomposition of diacetyl peroxide in pyridine.³⁷¹ The $\alpha:\beta:\gamma$ -ratio is about 3.5:1.2:1 irrespective of whether the source of methyl radicals is acetyl peroxide or lead tetracetate (in the absence of acetic acid).³⁷¹ The decomposition of more complex diacyl peroxides of the type $[\text{CH}_3\text{CO}_2-(\text{CH}_2)_n-\text{CH}_2\text{CO}_2]_2$ ($n = 1, 3$) in pyridine has been studied by

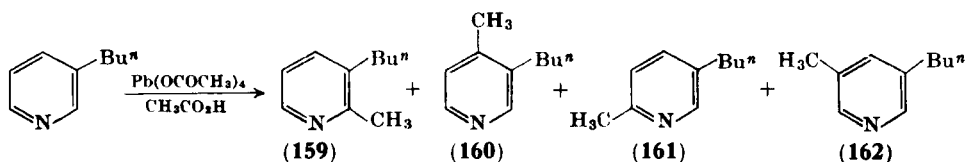
³⁶⁹ R. O. C. Norman and G. K. Radda, in "Advances in Heterocyclic Chemistry" (A. R. Katritzky, ed.), Vol. 2, p. 152. Academic Press, New York, 1963.

³⁷⁰ S. Goldschmidt and M. Minsinger, *Ber.* **87**, 956 (1954).

³⁷¹ R. A. Abramovitch and K. Kenaschuk, Unpublished results (1965).

Goldschmidt and Beer.³⁷² The 2-alkylated product is the main one formed. This orientation is not unexpected since, compared with the phenyl radical, an alkyl radical should have some "nucleophilic character." The β -/ γ - ratio is also lower than in the phenylation, as expected for a more nucleophilic radical.³⁷¹ Pyridine has a "methyl affinity" of 3 compared with benzene.³⁷³ This, however, does not represent the relative amount of picolines and toluene formed with acetyl peroxide.³⁷¹

The alkylation of 3-picoline by methyl radicals generated from lead tetraacetate has been reported³⁷⁴ to give a mixture of 2,3- and 2,5-lutidine. The other lutidines were undoubtedly also formed but not detected by the analytical method used. The possibility that, at least to a certain extent, it is a lead complex of pyridine that may be undergoing alkylation under these conditions cannot be discounted, but is unlikely in view of the results with pyridine. Certainly, in the acidic medium used, the pyridine is *N*-protonated to a large degree. A quantitative study of the methylation of 3-picoline using acetyl peroxide as the source of methyl radicals gave the following proportions of lutidines³⁷¹: 2,3- 55.5%; 2,5-, 19.4%; 3,4-, 20.5%; and 3,5- 4.6%. In connection with studies of possible synthetic approaches to fusaric acid, the alkylation of 3-*n*-butylpyridine with lead tetraacetate has been examined relatively systematically.³⁷⁵ The composition of the monomethylated products was determined by gas chromatography in combination with infrared spectroscopy. It is unfortunate that a large excess of 3-butylpyridine compared with the amount of lead tetraacetate was not used. The main product of monomethylation (60% of total) was 3-*n*-butyl-2-methylpyridine (**159**), while about equal amounts (slightly less than 20%) of each of the 4-



³⁷² S. Goldschmidt and L. Beer, *Ann.* **641**, 40 (1961).

³⁷³ M. Szwarc and J. H. Binks, in "Theoretical Organic Chemistry," p. 262. Butterworth, London and Washington, D.C., 1959.

³⁷⁴ W. H. Rieger, U.S. Patent 2,502,174 (1950); *Chem. Abstr.* **44**, 5396 (1950).

³⁷⁵ E. Hardegger and E. Nikles, *Helv. Chim. Acta* **40**, 2421 (1957).

(160) and 6-methyl (161) derivatives were obtained. About 2% of the total product was thought to consist of 3-*n*-butyl-5-methylpyridine (162). A small amount of the dimethylated 3-*n*-butylpyridines was obtained together with an appreciable quantity of a high-boiling residue.

TABLE XV
FREE RADICAL PHENYLATION OF PYRIDINE

| Radical source | Temperature | Isomer ratio (%) | | | Partial rate factors | | | Total rate ratio $\frac{Py}{C_6H_4}K$ |
|--|-------------|-------------------|------|------|----------------------|-------|-------|---------------------------------------|
| | | 2- | 3- | 4- | F_2 | F_3 | F_4 | |
| Benzoyl peroxide ^a | 105° | 54 | 32 | 14 | Not determined | | | Not determined |
| Benzoyl peroxide ^{b, c} | 80° | 58 | 28 | 14 | 1.8 | 0.87 | 0.87 | 1.04 |
| Lead tetra-benzoate ^a | 105° | 52 | 32 | 14 | — | — | — | — |
| Electrolysis of benzoic acid ^d | 15–20° | 56 | 35 | 9 | — | — | — | — |
| Photolysis of triphenyl-bismuth ^f | 100° | 48 | 31 | 21 | 1.7 | 1.1 | 1.5 | 1.18 ^e |
| Gomberg–Hey reaction ^g | 40° | 53.6 | 29.3 | 17.1 | 1.83 | 1.00 | 1.18 | 1.14 |
| Benzenediazonium ^h borofluoride | 40° | 51.8 | 32.4 | 15.7 | — | — | — | — |
| | 40° | 89.0 ⁱ | 11.0 | 0 | — | — | — | — |

^a Hey *et al.*³⁷⁶

^b Augood *et al.*³⁷⁷

^c Dannley and Gregg.³⁷⁸

^d Bunyan and Hey.³⁷⁹

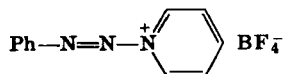
^e Measured at 80°.

^f Hey *et al.*³⁸⁰

^g Abramovitch and Saha.^{15, 16}

^h Abramovitch and Saha.^{380a}

ⁱ Using a benzene-diazonium borofluoride: pyridine molar ratio of 1:6. The reaction mixture is heterogeneous under these conditions. An intramolecular attack of the complexed pyridine nucleus may well be involved here.



³⁷⁶ D. H. Hey, C. J. M. Stirling, and G. H. Williams, *J. Chem. Soc.* **1955**, 3963.

³⁷⁷ D. R. Augood, D. H. Hey, and G. H. Williams, *J. Chem. Soc.* **1952**, 2094.

³⁷⁸ R. L. Dannley and E. C. Gregg, *J. Am. Chem. Soc.* **76**, 2997 (1954).

³⁷⁹ P. J. Bunyan and D. H. Hey, *J. Chem. Soc.* **1960**, 3787.

³⁸⁰ D. H. Hey, D. A. Shingleton, and G. H. Williams, *J. Chem. Soc.* **1963**, 5612.

^{380a} R. A. Abramovitch and J. G. Saha, *Tetrahedron* **21**, 3297 (1965).

The homolytic arylation of pyridine has been studied somewhat more systematically but by no means exhaustively. Quantitative analysis of the phenylation products using various sources of phenyl radicals has been achieved by ultraviolet spectroscopic or gas chromatographic methods. The results of some recent determinations are given in Table XV.

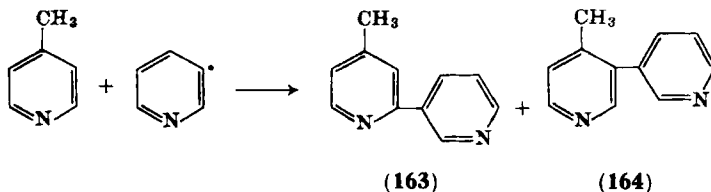
The reactivities of the three positions in pyridine toward homolytic phenylation are in the order predicted by molecular orbital calculations.¹⁴ With more "electrophilic" radicals, e.g., *o*-nitrophenyl, one would predict that the over-all reactivity would decrease and that more β -arylated product would be formed than in phenylation. The opposite would be true for more "nucleophilic" radicals, e.g., *p*-tolyl. These predictions have been substantiated experimentally^{15, 16} as is seen from the data in Table XVI. In fact, with the *o*-nitrophenyl radical, the β -position in pyridine is the most reactive one.

TABLE XVI
RELATIVE RATES OF ARYLATION OF PYRIDINE AT 40° AND PARTIAL
RATE FACTORS^a

| Radical: | Ph · | <i>o</i> -Me · C ₆ H ₄ · | <i>p</i> -Me · C ₆ H ₄ · | <i>o</i> -NO ₂ · C ₆ H ₄ · | <i>p</i> -NO ₂ · C ₆ H ₄ · |
|---------------------|------|--|--|---|---|
| $\frac{F_Y}{F_2} K$ | 1.14 | 1.72 | 1.44 | 0.47 | 0.78 |
| F_2 | 1.83 | 2.72 | 2.51 | 0.60 | 1.03 |
| F_3 | 1.00 | 1.53 | 1.13 | 0.71 | 1.00 |
| F_4 | 1.18 | 1.82 | 1.36 | 0.21 | 0.60 |

^a From Abramovitch and Saha.¹⁶

The effects of substituents upon the orientation of the entering phenyl radical and upon the reactivity of the pyridine nucleus have not received much attention. 4-Picoline is substituted by the 3-pyridyl radical (from the Gomberg-Hey reaction) to give a mixture containing 15% of the product of attack at the α -position (**163**) and 55% of product of attack at the β -position (**164**). A very similar result was



obtained when 4-ethylpyridine was the substrate.³⁸¹ Ethyl isonicotinate and the 3-quinolyl radical are said to give ethyl 2-(3'-quinolyl)isonicotinate.³⁸² The results obtained above with 4-picoline have now received support from accurate quantitative analysis by gas chromatography of the products obtained in the Gomberg-Hey phenylation of 4-picoline. The two possible phenyl-4-picolines were obtained, the mixture consisting of 44.9% of 2-phenyl-4-picoline and 55.1% of 3-phenyl-4-picoline ($C_{6H_5}^{Py}K = 1.39$, $F_2 = 1.87$, $F_3 = 2.30$). Again, it appears that the substituting group has a slight preference for the β - over the α -position.³⁸³ This is readily understandable on the basis of the principle of additivity of substituent effects: thus, $^{CH_3}F_0$ for the phenylation of toluene is 3.5 compared with $^{Py}F_2 = 1.83$ for the phenylation at C-2 of pyridine. That the methyl group will then control the substitution is not surprising. The phenylation of 3-picoline at 40° under Gomberg-Hey conditions again leads to all possible monophenylated products (Table XVII). Most of these

TABLE XVII
COMPETITIVE PHENYLATION OF 3-PICOLINE AT 40°

| Product | Isomer ratio (%) | Partial rate factor F_r | Total rate ratio (relative to benzene) |
|---------------------|------------------|---------------------------|--|
| 2-Phenyl-3-picoline | 43.3 | 3.54 | 1.36 ± 0.6 |
| 4-Phenyl-3-picoline | 28.7 | 2.34 | |
| 5-Phenyl-3-picoline | 6.9 | 0.56 | |
| 6-Phenyl-3-picoline | 21.1 | 1.72 | |

^a Abramovitch and Saha.³⁸³

results are again roughly rationalized on the basis of the additivity of the effects of the 3-methyl group and of the pyridine nitrogen atom. Unless one considers the phenyl radical as having "nucleophilic character," however, it is hard to find a ready explanation for the observed *deactivation* of C-5 in 3-picoline compared both with the same position in pyridine itself and with a position in benzene. It should be pointed out that F_m for toluene and for anisole is

³⁸¹ R. L. Frank and J. V. Crawford, *Bull. Soc. Chim. France* **1958**, 419.

³⁸² D. H. Hey and J. M. Williams, *J. Chem. Soc.* **1950**, 1678.

³⁸³ R. A. Abramovitch and M. Saha, *Can. J. Chem.* In press (1966).

< 1 .^{383a} It seems unlikely, at this time, that the rate-determining step in these reactions is the formation of a non-localized π -complex rather than the more usually accepted σ -complex. If this were the case, however, it would render the partial rate factors meaningless as indices of relative reactivities.

The radical hydroxylation of pyridine has not been studied, but the substitution of quinoline by hydroxyl radicals produced under various conditions has been investigated.³⁸⁴⁻³⁸⁶ The main, if not exclusive, product is 3-hydroxyquinoline, a result understandable in terms of an "electrophilic" hydroxyl radical. Persulfate oxidation of 2-pyridone in alkaline solution in the presence of ferrous ion (modified Elbs oxidation) gives 5-hydroxy-2-pyridone as the major product together with some 3-hydroxy-2-pyridone.³⁸⁷ The dominant influence of the hydroxyl substituent is supported, in this case, by the pyridine nitrogen atom (which, presumably, would direct a hydroxyl radical or sulfate ion radical $\cdot\text{OSO}_3^-$ to the β -position if the reaction with quinoline is made to serve as an indicator). In 3-hydroxypyridine the directing effects of the two functional groups clash if the attacking species did indeed have electrophilic character. This is actually found to be the case, for hydroxylation of 3-hydroxypyridine under normal Elbs oxidation conditions (no Fe^{2+}) led mainly to 5-hydroxy-2-pyridone (the attacking $\cdot\text{OSO}_3^-$ entering *para* to the phenolic group already present) together with minor amounts of 3-hydroxy-2-pyridone and 3-hydroxy-4-pyridone. No product of substitution at C-5 was reported.³⁸⁷ It has been suggested, however, that this is not a homolytic process at all but that it involves a concerted electrophilic attack by the persulfate anion.³⁸⁸

The halogenation of pyridine and some of its derivatives at high temperatures in the gaseous phase has been the object of numerous studies, first by Wibaut and then by den Hertog and their respective

^{383a} R. T. Morrison, J. Cazes, N. Samkoff, and C. A. Howe. *J. Am. Chem. Soc.* **84**, 4152 (1962).

³⁸⁴ R. Breslow and L. N. Lukens, *J. Biol. Chem.* **235**, 292 (1960).

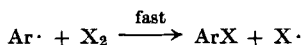
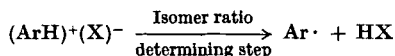
³⁸⁵ B. B. Brodie, J. Axelrod, P. A. Shore, and S. Udenfriend, *J. Biol. Chem.* **208**, 741 (1954).

³⁸⁶ C. Mitoma, H. S. Posner, H. C. Reitz, and S. Udenfriend, *Arch. Biochem. Biophys.* **61**, 431 (1956).

³⁸⁷ E. J. Behrman and B. M. Pitt, *J. Am. Chem. Soc.* **80**, 3717 (1958).

³⁸⁸ W. A. Waters, "Mechanisms of Oxidation of Organic Compounds," p. 136. Methuen, London, 1964.

schools. While the gas-phase chlorination (in a vessel packed with pumice or graphite as contact substance) of pyridine at 220° gives the normal orientation expected for electrophilic substitution, at 270–400° the products obtained are 2-chloro- and 2,6-dichloropyridine.³⁸ A similar change in orientation is observed in bromination when the temperature is raised from 300° to 500°. At the higher temperature the 2- and 2,6-dibromopyridines are formed.^{38,9} Unfortunately, quantitative data on the ratios of the isomeric chloro- and bromopyridines are not yet available. In the temperature range 320–420°, the vapor-phase chlorination of pyridine takes place with much greater violence than the bromination, and charring occurs. The unusual orientation observed at the higher temperatures has been attributed to a change in the mechanism of halogenation, from a straightforward electrophilic mode of attack to a (probably) free-radical process involving attack, conceivably, by bromine atoms.¹ Kooyman has carried out a systematic study of the high temperature gas-phase halogenation of benzene derivatives^{39,0} and has found that (i) substitution takes place preferentially at positions of lowest reactivity to electrophilic substitution; (ii) oxygen, nitric oxide, or iodine have little effect on rates or orientation; (iii) chlorination and bromination give rise to similar isomer ratios and to the same H/D isotope effect; (iv) the over-all chlorination rates decrease in the order PhO, H, (F, Cl), CN of substituents present in the nucleus. On this basis, he proposed the tentative mechanism shown in Scheme X, involving the formation of an ion-pair intermediate ArH^+X^- or ArH^+X_2^- :



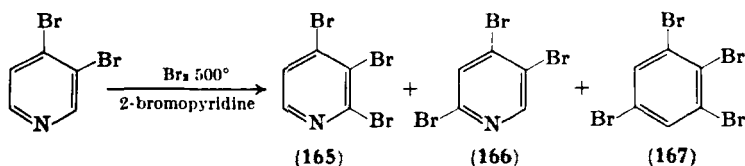
SCHEME X

Substituent effects on the proton-losing step would then be responsible for the isomer-distribution pattern. A similar picture could be drawn for the high temperature gas-phase halogenation of pyridines.

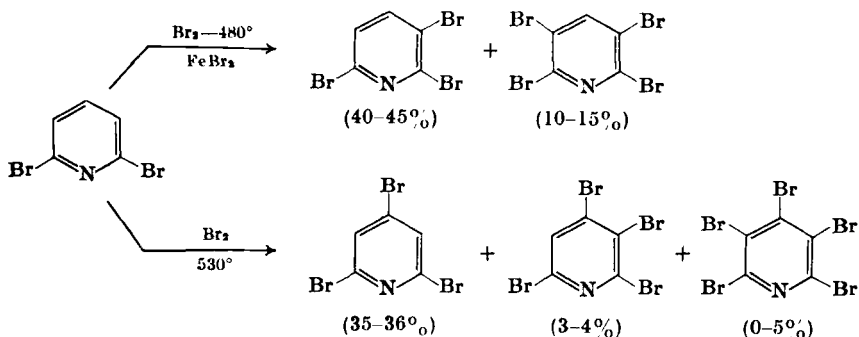
^{38,9} H. J. den Hertog and J. P. Wibaut, *Rec. Trav. Chim.* **51**, 381 (1932).

^{39,0} E. C. Kooyman, in "Congress Lectures, XIXth International Congress of Pure and Applied Chemistry, London, 1963," p. 193. Butterworth, London and Washington, D.C., 1963.

Bromination of 2-bromopyridine at 500° gives, as expected, 2,6-dibromopyridine.⁵¹ Difficulty was encountered when the bromination of 3,4-dibromopyridine under these conditions was studied, because of the formation of pyridinium salts from the reactive 4-bromo compound. When 2-bromopyridine was used as a solvent, these difficulties were circumvented and 2,3,4- (165) and 2,4,5-tribromopyridine (166), and 2,3,4,6-tetrabromopyridine (167) were isolated.⁵¹



3,4,5-Tribromopyridine gave a mixture of 2,3,4,5-tetrabromo- and 2,3,4,5,6-pentabromopyridine. The bromination of 2,6-dibromopyridine at various temperatures between 450° and 550° , in the presence or absence of ferrous bromide or cuprous bromide, has been studied.³⁹¹ Scheme XI illustrates some of the results obtained. At



SCHEME XI

530° , no 2,3,6-tribromopyridine was detected. Conversion of 2,6-dibromopyridine into the 2,4,6-tribromo compound shows a rather high temperature coefficient. The amount of attack at C-4 was enhanced by the presence of iodine but yields were not affected by ultraviolet irradiation of the reaction mixture.

³⁹¹ H. J. den Hertog, W. P. Combé, and C. R. Kolder, *Rec. Trav. Chim.* **77**, 66 (1958).

The gas-phase bromination (500°) of 2-aminopyridine was first studied by Wibaut and den Hertog^{393,392} and then under more controlled conditions (atmosphere of nitrogen, pumice contact surface) by den Hertog and Bruin.⁸⁵ No attack at C-4 was observed. About equal proportions (qualitatively) of 3-bromo, 5-bromo, and 6-bromo-2-aminopyridine were obtained, together with smaller amounts of 3,6- and 5,6-dibromo-2-aminopyridine. Occasionally 3,5-dibromo- and 3,5,6-tribromo-2-aminopyridine could also be isolated. Using an empty tube (no pumice), the products of bromination were 5-bromo- (main), 3,5-dibromo-, and 3,5,6-tribromo-2-aminopyridine. Once again the dominating influence of the amino group upon orientation is clear and suggests that in this particular case the mechanism of bromination may be different from that proposed by Kooyman for the benzene series.

Homolytic substitution of pyridinium salts has scarcely been studied. The phenylation of pyridine in acetic acid solution by benzene-diazonium borofluoride has been reported,^{392a} as has the phenylation of pyridine-metal complexes.^{392b}

B. PYRIDINE *N*-OXIDES

The free-radical arylation of pyridine *N*-oxides has not been studied systematically, alkylation not at all. When pyridine *N*-oxide was treated with benzene- and *p*-chlorobenzenediazonium salts only the 2-arylpyridine *N*-oxides were isolated.³⁹³ No mention was made of the formation of the 3- and 4-aryl derivatives expected to be produced as well. The phenylation of pyridine *N*-oxide (diazoaminobenzene at 131° or 181° was found to be the most convenient source of phenyl radicals) was reinvestigated,³⁹⁴ and the reactivities of the nuclear positions found to be in the order 2 > 4 > 3, which is also that predicted⁶ on the basis of atom localization energy calculations. 2-Phenylpyridine *N*-oxide formed 71–81% of the total phenylation products, whereas the 3-isomer comprised only 5.6–9.6% of that total. The phenylpyridines were found among the by-products of the reaction.

³⁹² J. P. Wibaut and H. J. den Hertog, *Ned. Octrooi* **1932**, 29614.

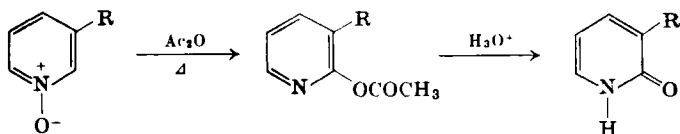
^{392a} H. J. M. Dou and B. M. Lynch, *Tetrahedron Letters* **1965**, 897.

^{392b} R. J. Gritter and A. W. Godfrey, *J. Am. Chem. Soc.* **86**, 4724 (1964).

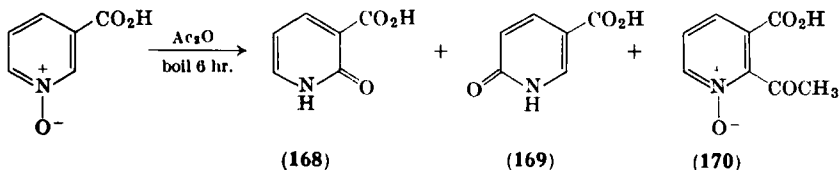
³⁹³ M. Colonna, *Atti Accad. Nazl. Lincei, Rend. Classe Sci. Fis., Mat. Nat.* **26**, 39 (1959); *Chem. Abstr.* **53**, 21929 (1959).

³⁹⁴ L. K. Dyall and K. H. Pausacker, *J. Chem. Soc.* **1961**, 18.

Controversy still exists concerning the mechanism of the reaction of pyridine *N*-oxides with acid anhydrides. The balance of opinion appears to favor a radical pathway as opposed to one involving nucleophilic attack (except perhaps for those cases where no alkyl group is present at C-2 or C-4) so that it is appropriate to discuss this reaction under the present heading without segregating it into a portion dealing with nucleophilic substitution and one with radical substitution. The earlier work has been summarized already³⁹⁵ and only a few points relevant to mechanism and orientation will be repeated here. When pyridine *N*-oxide is heated with acetic anhydride at 140–150°, 2-pyridyl acetate is formed first; it is then hydrolyzed to 2-pyridone.³⁹⁶ 3-Picoline *N*-oxide was said to be converted exclusively to the 2-pyridone³⁹⁷ and 3-fluoro-, 3-chloro-, and 3-bromopyridine *N*-oxide also give the 3-halo-2-pyridone, no 2,5-isomer being formed.³⁹⁸ 3-Nitropyridine *N*-oxide behaves similarly.³⁴⁶ On the



other hand, nicotinic acid *N*-oxide and acetic anhydride gave a 10% yield of 2-pyridone-3-carboxylic acid (**168**), 3% of 2-pyridone-5-carboxylic acid (**169**), and 25–30% of 2-acetylnicotinic acid *N*-oxide (**170**).³⁵⁹ It was suggested that **170** arose from an intramolecular rearrangement of the mixed anhydride **171**. The isolation of both **168** and **169** led to the reinvestigation of the reaction with 3-picoline *N*-oxide. Both pyridones were obtained in about equal amounts

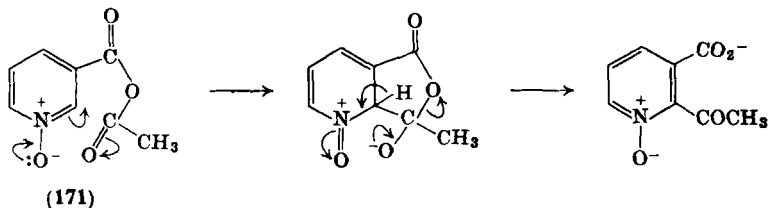


³⁹⁵ E. N. Shaw, in "Pyridine and Its Derivatives" (E. Klingsberg, ed.), Pt. II, Chapter V, p. 97. Wiley (Interscience), New York, 1961.

³⁹⁶ M. Katada, *J. Pharm. Soc. Japan* **67**, 51 (1947); *Chem. Abstr.* **45**, 9536 (1951).

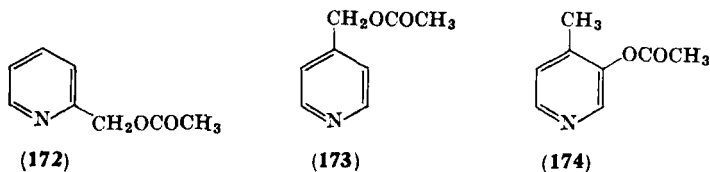
³⁹⁷ V. Boekelheide and W. J. Linn, *J. Am. Chem. Soc.* **76**, 1286 (1954).

³⁹⁸ M. P. Cava and B. Weinstein, *J. Org. Chem.* **23**, 1616 (1958).



(35–40%) together with 3-methyl-*N*-(5'-methyl-2'-pyridyl)-2-pyridone (152) (4%).³⁵⁹ The mechanism of formation of 152 from 3-picoline *N*-oxide and 2-acetoxy-3-picoline has already been discussed (Section IV, A, 3). 3-Hydroxypyridine gives a moderate yield of the 2- but not the 6-pyridone.³⁵⁹ The carboxylic esters all give pyridones as well. Methyl picolinate *N*-oxide gives the 6-pyridone (34%), methyl nicotinate *N*-oxide gives the 2- (28%) and the 6-pyridones (16%), and methyl-isonicotinate *N*-oxide forms the 2-pyridone (56%).³⁹⁹ 2-Cyanopyridine *N*-oxide does not react with acetic anhydride, but picolinic acid *N*-oxide undergoes ready decarboxylation.³⁹⁹ Isonicotinic acid *N*-oxide gives a small yield of the 2-pyridone, the main product being isonicotinic acid. A small amount of a compound $C_9H_9NO_4$ of unknown structure was also obtained.³⁵⁹ The 2-propionyl ketone corresponding to 170 was obtained (5%) together with 168 and 169 from the reaction of nicotinic acid *N*-oxide with propionic anhydride.

With alkyl groups in the 2- or 4-positions, however, the reaction may take a completely different course, resulting in side-chain oxidation. Thus, when 2-picoline *N*-oxide is heated with acetic anhydride, some 6-methyl-2-pyridone is indeed formed, but the main product is 2-pyridylmethyl acetate (172).^{397, 400} 4-Picoline *N*-oxide and acetic anhydride give 4-pyridylmethyl acetate (173) and 3-acetoxy-4-picoline (174) (65% yield) in the ratio of 9:1,^{362, 401}



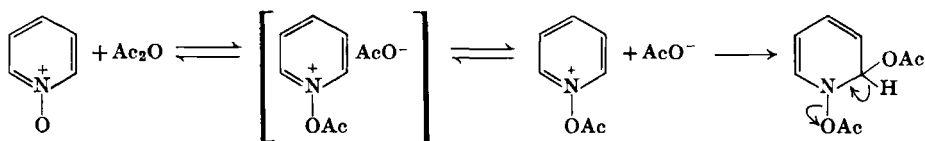
³⁹⁹ V. Boekelheide and W. L. Lehn, *J. Org. Chem.* **26**, 428 (1961).

⁴⁰⁰ O. H. Bullitt, Jr., and J. T. Maynard, *J. Am. Chem. Soc.* **76**, 1370 (1954).

⁴⁰¹ J. A. Berson and T. Cohen, *J. Am. Chem. Soc.* **77**, 1281 (1951).

together with minor amounts of 4-picoline (2.9%), 2,4-lutidine (0.2%), and 4-ethylpyridine (0.6%).³⁶² Similar products arose from the reaction of 4-picoline *N*-oxide and butyric anhydride.³⁶² The mechanism of the reaction of 2-alkylpyridine *N*-oxides with acetic anhydride has been studied further.^{401a}

2-Picoline *N*-oxide and phenylacetic anhydride in refluxing benzene gave 2-pyridylmethyl phenylacetate (32.2%), carbon dioxide (15%), β -phenyl-2-ethylpyridine (15%), and a mixture (3.3%) of what were probably 3-benzyl- and 5-benzyl-2-picoline. 4-Picoline *N*-oxide and phenylacetic anhydride gave a mixture containing 4-pyridylmethyl phenylacetate and 3-phenylacetoxy-4-picoline (2.5%), together with carbon dioxide (28.4%), β -phenyl-4-ethylpyridine (6.5%), 2-benzyl-4-picoline (1.9%), and 3-benzyl-4-picoline (0.9%).^{402, 403} The ring alkylation products are thought to arise from attack by free alkyl radicals produced by decarboxylation of acyloxy radicals presumably formed. A complete discussion of the various proposals concerning the mechanisms of these reactions is beyond the scope of this review and only the more recent references are given.^{362, 402, 404-408} The reaction of pyridine *N*-oxide with acetic anhydride exhibits pseudo first-order kinetics, and has been written as a nucleophilic substitution (Scheme XII);⁴⁰⁸ although a "caged radical" process was not ruled out, it was thought unlikely since it



SCHEME XII

^{401a} V. J. Traynelis and P. L. Pacini, *J. Am. Chem. Soc.* **86**, 4917 (1964).

⁴⁰² T. Cohen and J. H. Fager, *Abstr. 19th Intern. Congr. Pure Appl. Chem., London, 1963* A1-147; *J. Am. Chem. Soc.* **87**, 5701 (1965).

⁴⁰³ T. Cohen, Private communication (1964).

⁴⁰⁴ V. J. Traynelis and R. F. Martello, *J. Am. Chem. Soc.* **80**, 6590 (1958).

⁴⁰⁵ V. J. Traynelis, Sr. A. N. Gallagher, and R. F. Martello, *J. Org. Chem.* **26**, 4365 (1961).

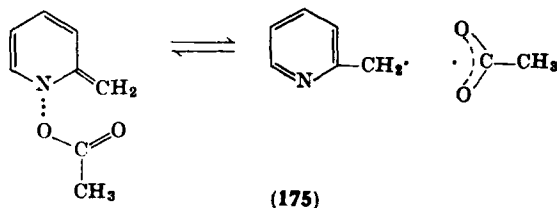
^{405a} V. J. Traynelis and Sr. A. N. Gallagher, *J. Am. Chem. Soc.* **87**, 5701 (1965).

⁴⁰⁶ S. Oae, T. Kitao, and Y. Kitaoka, *J. Am. Chem. Soc.* **84**, 3359 (1962).

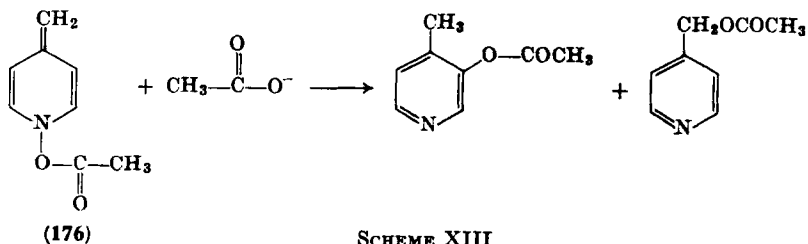
⁴⁰⁷ S. Oae, T. Kitao, and Y. Kitaoka, *J. Am. Chem. Soc.* **84**, 3362 (1962).

⁴⁰⁸ J. H. Markgraf, H. B. Brown, Jr., S. C. Mohr, and R. G. Peterson, *J. Am. Chem. Soc.* **85**, 958 (1963).

would involve the generation of a pyridyl radical cation, and no methane nor carbon dioxide was evolved except at temperatures higher than 130°. If this is, indeed, a nucleophilic substitution upon the pyridinium cation, as indeed it appears to be,^{408a} then it joins the lengthening list of such reactions in which a 3-substituent directs the entering group predominantly to C-2, irrespective of whether the substituent is electron-attracting (e.g., NO₂) or -donating (e.g., OH). The evidence for the formation of "caged" radicals in the reactions of the picoline *N*-oxides is, however, quite strong. The evidence in support of the proposal that 2-picoline *N*-oxide and acid anhydrides react mainly via a "free-radical pair" within a solvent cage (175)⁴⁰⁶



seems convincing^{408b}; some of the radicals occasionally escape from the cage and are then capable of being trapped.⁴⁰⁴ The results of O¹⁸-labeling experiments in the reaction with 4-picoline *N*-oxide have been interpreted as supporting a nucleophilic mode of attack of acetate upon 176 (Scheme XIII).⁴⁰⁷ These observations have been reinterpreted in terms of a radical-pair mechanism in which each step *except*

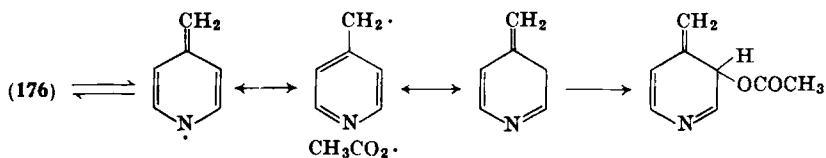


the product-forming step is reversible in the 4-case but not in the 2-case (Scheme XIV).^{402, 403, 405a} Support for this last proposal has been added from a comparison of the behavior of phenylacetic anhydride and

^{408a} S. Oae and S. Kozuka, *Tetrahedron* **20**, 2691 (1964).

^{408b} S. Oae, Y. Kitaoka, and T. Kitao, *Tetrahedron* **20**, 2685 (1964).

acetic anhydride ($\text{C}_6\text{H}_5\text{CH}_2\text{CO}_2\cdot$, which can give the relatively stable benzyl radical, has a much greater tendency to undergo loss of CO_2 than does $\text{CH}_3\text{CO}_2\cdot$). More recent ^{18}O studies combined with the investigation of the effects of solvents in the reaction of 4-picoline with acetic anhydride and with butyric anhydride has led to the conclusion that the mechanism may involve varying combinations of an intermolecular heterolytic process, an intermolecular homolytic reaction, and a radical cage pathway.^{408b,c} It should be pointed out that a species such as **176** cannot be formed from those pyridine *N*-oxides which do not bear a suitable alkyl group at the α - or γ -position.



SCHEME XIV

VI. Intramolecular Cyclizations

Due to difficulties expected and often found in attempted intramolecular cyclizations onto a pyridine ring, particularly by processes involving an electrophilic mode of attack, not too many such reactions have been reported, though many of the common cyclization reactions that can be effected in the benzene series have been tried at least in the pyridine series.

Fischer cyclization onto a pyridine ring has met with varied results. In some cases no cyclization products could be obtained, whereas in others cyclization could be effected in high yield, albeit using more vigorous conditions than are necessary to effect ring-closure onto a benzene ring. Perkin and Robinson⁴⁰⁹ were unable to cyclize acetone 2-quinolylhydrazone under a variety of conditions and catalysts. Negative results were also obtained with a number of 2-pyridylhydrazones.⁴¹⁰ Even under very stringent conditions the 2-pyridylhydrazones of acetaldehyde, acetone, and pyruvic acid in polyphosphoric acid resisted cyclization.⁴¹¹ In contrast to this, cyclo-

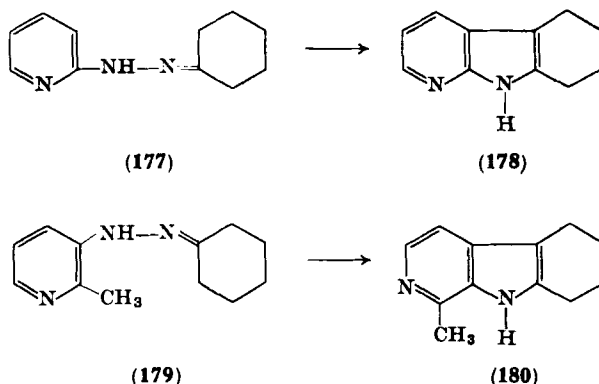
^{408c} S. Oae, Y. Kitaoka, and T. Kitao, *Tetrahedron* **20**, 2677 (1964).

⁴⁰⁹ W. H. Perkin, Jr., and R. Robinson, *J. Chem. Soc.* **1913**, 1973.

⁴¹⁰ R. G. Fargher and R. Furness, *J. Chem. Soc.* **1915**, 688.

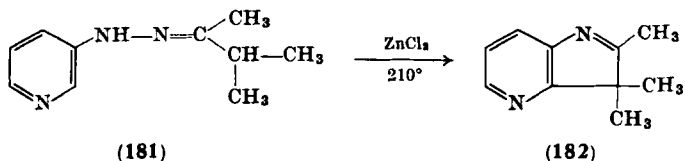
⁴¹¹ S. Okuda and M. M. Robison, *J. Am. Chem. Soc.* **81**, 740 (1959).

hexanone 2-pyridylhydrazone (177) gave 5,6,7,8-tetrahydro- α -carboline (178) in 53% yield on heating in polyphosphoric acid.⁴¹¹ Cyclohexanone-2-methyl-3-pyridylhydrazone (179) yielded a small amount of 1-methyl-5,6,7,8-tetrahydro- β -carboline (180) on heating with zinc chloride.⁴¹² No ambiguity concerning the site of cyclization is possible in either case. The cyclization of isopropyl methyl ketone 2-pyridylhydrazone required heating with zinc chloride at 250° to



give 2,3,3-trimethyl-7-azaindole,⁴¹³ whereas the cyclization of the corresponding phenylhydrazone could be effected by heating it under reflux with zinc chloride in ethanol.⁴¹⁴

The ring-closure of isopropyl methyl ketone 3-pyridylhydrazone (181) is said to give exclusively 2,3,3-trimethyl-4-azaindole (182),⁴¹³ whereas acetone 2-chloro-5-pyridylhydrazone gives 5-chloro-2-methyl-4-azaindole.⁴¹⁵ No product of attack at the γ -position was reported.



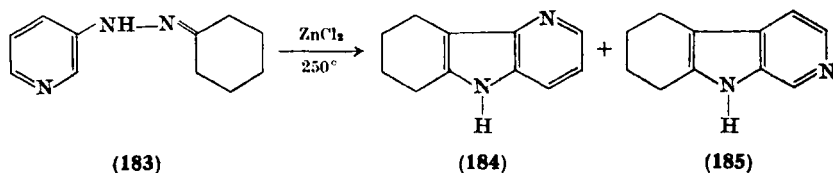
⁴¹² G. R. Clemons and R. J. W. Holt, *J. Chem. Soc.* **1953**, 1313.

⁴¹³ G. E. Ficken and J. D. Kendall, *J. Chem. Soc.* **1959**, 3202.

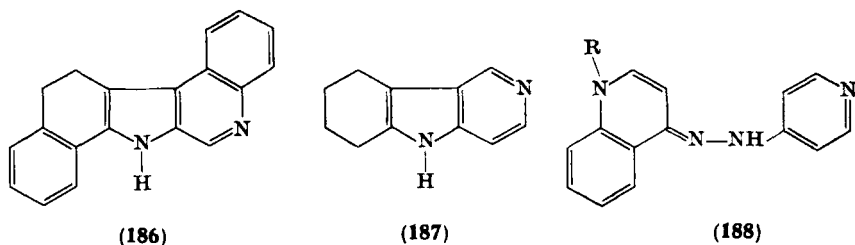
⁴¹⁴ G. Plancher, *Ber.* **31**, 1488 (1898).

⁴¹⁵ T. Takahashi, H. Saikachi, H. Goto, and S. Shimamura, *J. Pharm. Soc. Japan* **64**, 7 (1944); *Chem. Abstr.* **45**, 8529 (1951).

On the other hand, the Fischer cyclization of cyclohexanone 3-pyridylhydrazone (**183**) gave a mixture (94% yield) of 6,7,8,9-tetrahydro- δ -carboline (**184**) and 5,6,7,8-tetrahydro- β -carboline (**185**).⁴¹⁶ The ratio of **184** to **185** was 63:37, cyclization at the α -position taking place with greater ease than at the γ -position. The 3-quinolylhydrazone of α -tetralone gave only one product on heating with zinc



chloride in *p*-cymene, and this has been assumed to be 12,13-dihydro-7*H*-dibenz[*c,i*]- β -carboline (**186**) by analogy with the cyclization of ethyl pyruvate 3-quinolylhydrazone which gave 3*H*-pyrrolo[2,3-*c*]-quinoline.⁴¹⁷ Cyclohexanone 4-pyridylhydrazone gave 5,6,7,8-tetrahydro- γ -carboline (**187**) on heating with zinc chloride at 240° for 10



minutes, but the cyclization of the 4-quinolone 4'-pyridylhydrazone (**188**) could not be effected, the hydrazone either being recovered or partially decomposed.⁴¹⁸

The thermal cyclizations of the 2-pyridylhydrazones of cyclohexanone and benzyl phenyl ketone have been effected in good yield.^{418a} In the absence of the acid catalyst, the pyridine ring is not protonated and is, therefore, more susceptible to electrophilic attack.

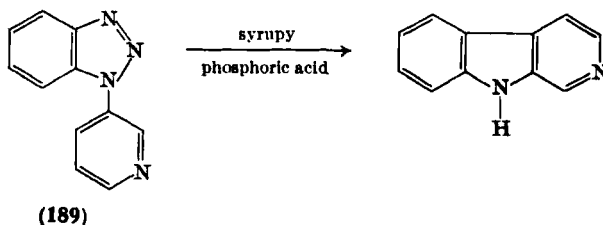
⁴¹⁶ R. A. Abramovitch and K. A. H. Adams, *Can. J. Chem.* **40**, 864 (1962).

⁴¹⁷ T. R. Govindachari, S. Rajappa, and V. Sudarsanam, *Tetrahedron* **16**, 1 (1961).

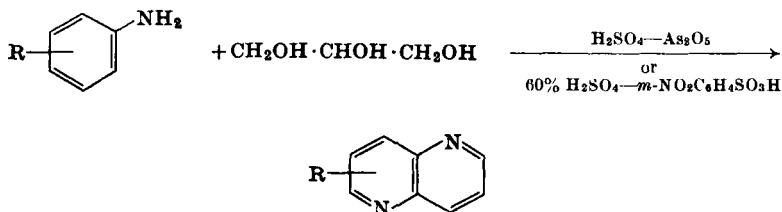
⁴¹⁸ F. G. Mann, A. F. Prior, and T. J. Willcox, *J. Chem. Soc.* **1959**, 3830.

^{418a} A. H. Kelly, D. H. McLeod, and J. Parrick, *Can. J. Chem.* **43**, 296 (1965).

The application of the Graebe-Ullmann carbazole synthesis to the carboline series has led to syntheses of α -, β -, and γ -carboline. This reaction has already been reviewed in Vol. III of this series.⁴¹⁹ The only point worth reemphasizing at this stage is the fact that Graebe-Ullmann cyclization of 1- β -pyridylbenztriazole (**189**) gives mainly, if not only, β -carboline—cyclization taking place at C-4 of the pyridine ring—in marked contrast to the results obtained in the Fischer cyclizations.



The Skraup reaction is successful with 3-aminopyridines but fails with 2- and 4-aminopyridines (although it has been successful with 4-aminoquinaldine⁴²⁰). The product of cyclization at the α -position is invariably obtained in the Skraup reaction with 3-aminopyridines. Thus, 3-aminopyridine itself gives 1,5-naphthyridine,⁴²¹ and various substituted 3-aminopyridines give the corresponding 1,5-naphthyridines. In only one case has a 1,7-naphthyridine been isolated.^{422, 423, 423a}



⁴¹⁹ R. A. Abramovitch and I. D. Spenser, in "Advances in Heterocyclic Chemistry" (A. R. Katritzky, ed.), Vol. 3, p. 79. Academic Press, New York, 1964.

⁴²⁰ F. Lions and E. Ritchie, *J. Proc. Roy. Soc. N.S. Wales* **74**, 443 (1941); *Chem. Abstr.* **35**, 4771 (1941).

⁴²¹ A. Albert, *J. Chem. Soc.* **1960**, 1790.

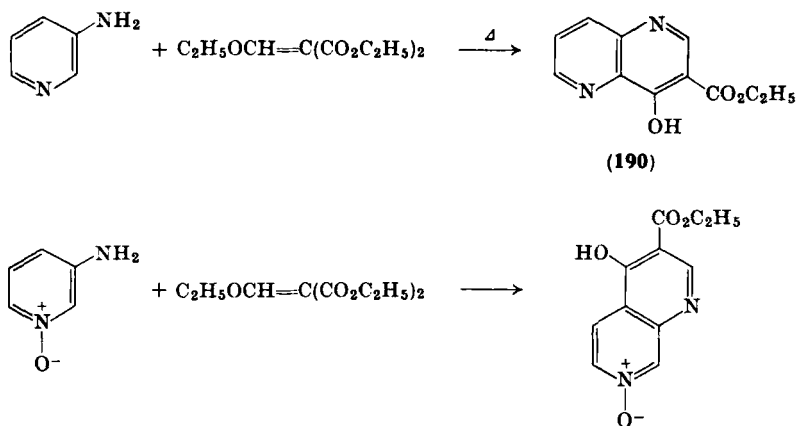
⁴²² W. Czuba, *Rec. Trav. Chim.* **82**, 988 (1963).

⁴²³ M. J. Weiss and C. R. Hauser, in "Heterocyclic Compounds" (R. C. Elderfield, ed.), Vol. 7, Chapter 2, p. 198. Wiley, New York, 1961.

^{423a} A. Albert and A. Hampton, *J. Chem. Soc.* **1952**, 4985.

When 3-aminopyridine *N*-oxide was subjected to the conditions of the Skraup reaction, 1,5-naphthyridine itself was obtained, presumably due to prior deoxygenation of the starting material followed by cyclization.⁴²⁴

The almost exclusive ring closure at the α -position carries over to other electrophilic reactions of substituted 3-aminopyridine derivatives. For example, the condensation of 3-aminopyridine with ethoxymethylenemalonate (EMME) in dilute solution in boiling Dowtherm A gave the 1,5-naphthyridine **190**.^{425, 426} The only exception to date is that of 3-aminopyridine *N*-oxide which, as expected,



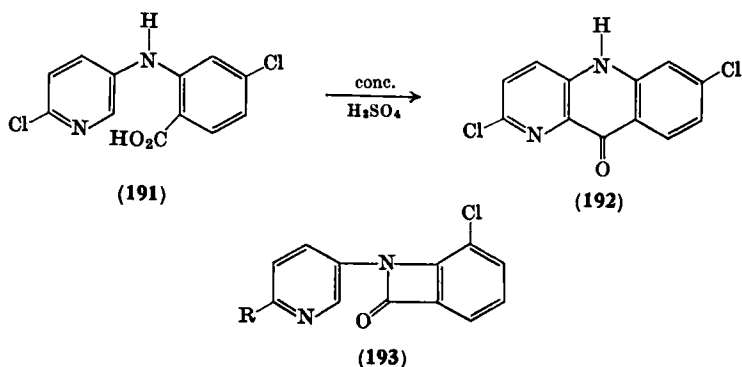
prefers to undergo cyclization at the 4-position in the EMME method, the *N*-oxide function directing the mode of electrophilic attack.⁴²⁴ This and other reactions of 3-aminopyridines such as the Knorr, Conrad-Limpach, Combes, and Doebner-Miller reactions have been reviewed.⁴²³

Intramolecular acylations of the Friedel-Crafts type will also take place with 3-aminopyridine derivatives but usually require either stringent conditions or the presence of further activating groups in the pyridine nucleus. The report that the acid **191** can be converted into

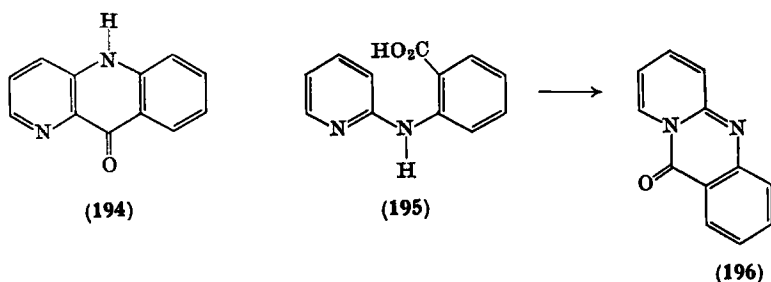
⁴²⁴ J. G. Murray and C. R. Hauser, *J. Org. Chem.* **19**, 2008 (1954).

⁴²⁵ C. C. Price and R. M. Roberts, *J. Am. Chem. Soc.* **68**, 1204 (1946).

⁴²⁶ J. T. Adams, C. K. Bradsher, D. S. Breslow, S. T. Amore, and C. R. Hauser, *J. Am. Chem. Soc.* **68**, 1317 (1946).



the benznaphthyridone **192** with concentrated sulfuric acid⁴²⁷ needs confirmation. *N*-3'- and *N*-4'-pyridylanthranilic acids are not cyclized by the usual reagents (POCl_3 or concentrated H_2SO_4).⁴²⁸⁻⁴³⁰ On the other hand, *N*-3'-pyridyl-4-chloroanthranilic acid was reportedly cyclized to 6-chloro-9-hydroxypyrido[3,2-*b*]quinoline with concentrated sulfuric acid.⁴²⁵ The structure of the product was not proved but was assumed on the basis of the fact that the Skraup and related reactions give products of cyclization at the α -position. Replacement of the hydroxyl group by chlorine could not be effected in this compound and further work seems necessary to establish whether it is a naphthyridine or an azetidone derivative (**193**, $\text{R} = \text{H}$).⁴³¹ Cyclization of *N*-3'-pyridylanthranilic acid to pyrido[3,2-*b*]quinolin-10(5*H*)-one (**194**) has now been achieved by heating it with



⁴²⁷ T. Takahashi and H. Hayase, *J. Pharm. Soc. Japan* **65**, 9 (1945); *Chem. Abstr.* **45**, 8530 (1951).

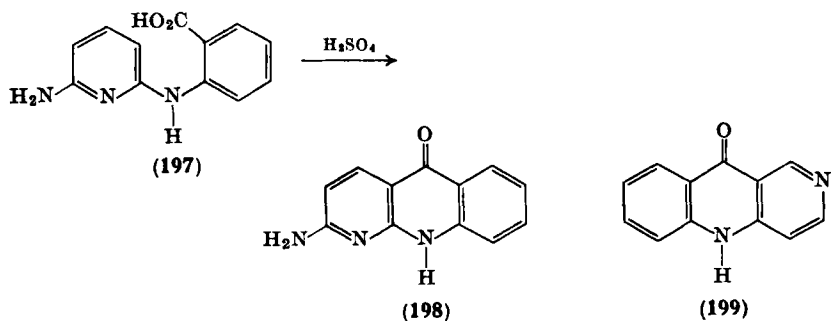
⁴²⁸ W. O. Kermack and A. P. Weatherhead, *J. Chem. Soc.* **1942**, 726.

⁴²⁹ V. Petrow, *J. Chem. Soc.* **1945**, 927.

⁴³⁰ G. B. Bachman and R. S. Barker, *J. Org. Chem.* **14**, 97 (1949).

⁴³¹ V. Petrow and B. Sturgeon, *J. Chem. Soc.* **1949**, 1157.

aluminum chloride-sodium chloride melt at 230–240°. No cyclization to C-4 of the pyridine ring was encountered.⁴³² While *N*-2'-pyridylanthranilic acid (**195**) cyclizes onto the pyridine nitrogen atom to give **196** and no azaacridone is formed,⁴³³ a 6-amino group in the pyridine nucleus facilitates ring closure at the β -position (**197**→**198**).⁴³⁴ *N*-4'-Pyridylanthranilic acid has also been cyclized to the azaacridone **199** with aluminum chloride sodium chloride melt.⁴³⁵



The application of the ethoxymethylenemalonic ester method to 4-aminopyridine leads to the formation of 1,6-naphthyridine, whose structure is unambiguous.⁴³⁶ Due to the low basicity of 4-aminopyridine, however, the Knorr, Conrad-Limpach, and Combes reactions fail with this compound. The EMME method has been used successfully with 2-aminopyridines. Cyclization can occur either at the nitrogen atom or at the β -position in this case and, unless the pyridine nucleus contains an activating substituent, a pyrimidine will be formed by attack at the electron-rich nitrogen atom. A 1,8-naphthyridine (**201**) is formed in good yield from 2-aminopyridines (**200**) when R is 6-amino,⁴²⁶ 6-methyl, or 6-ethoxy,⁴³⁷ whereas the pyrimidine (**202**) is produced when R is 4-methyl, 5-methyl, 5-chloro, 5-bromo, or 4-ethoxy.⁴³⁷ Only tars were formed when R = H. Similar results have been obtained when the amides from 2-aminopyridine derivatives and diethyl malonate are cyclized. This reaction as well as

⁴³² R. E. Corbett and B. J. Sweetman, *J. Chem. Soc.* **1963**, 6058.

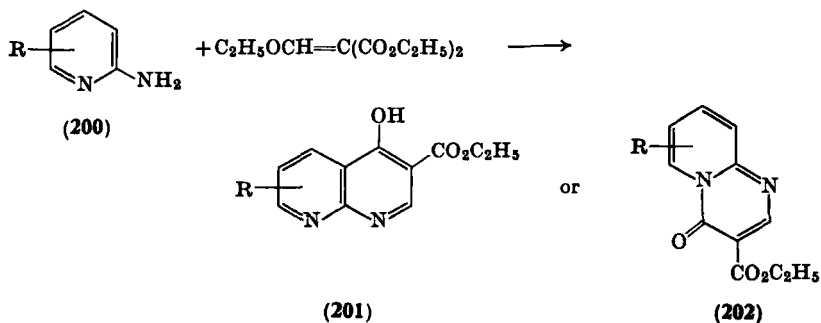
⁴³³ O. Seide, *Ann.* **440**, 311 (1924).

⁴³⁴ M. I. Kabachnik, *J. Gen. Chem. USSR* **9**, 1734 (1939); *Chem. Abstr.* **34**, 3748 (1940).

⁴³⁵ B. M. Ferrier and N. Campbell, *Chem. Ind. (London)* **1958**, 1089.

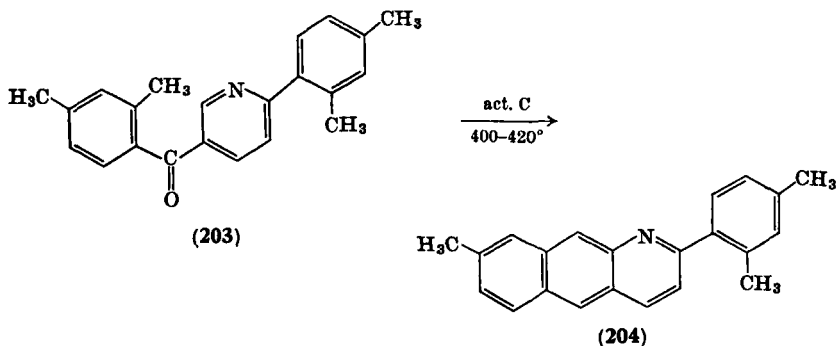
⁴³⁶ C. R. Hauser and G. A. Reynolds, *J. Org. Chem.* **15**, 1224 (1950).

⁴³⁷ G. R. Lappin, *J. Am. Chem. Soc.* **70**, 3348 (1948).



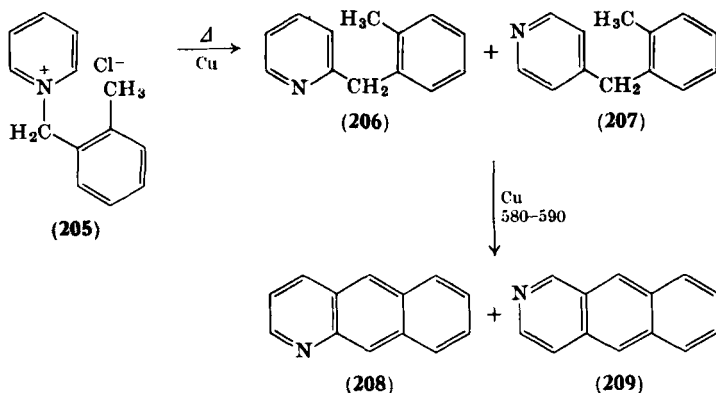
the Knorr, Conrad-Limpach, and Combes reactions with 2-amino-pyridines have been reviewed.⁴²³

The Elbs reaction has been made use of occasionally to effect intramolecular cyclization onto a pyridine ring. 2-(2',4'-Dimethylphenyl)-5-(2'',4''-dimethylbenzoyl)pyridine (203) underwent cyclization when its vapors were passed over activated carbon at 400–420° and gave 2-(2',4'-dimethylphenyl)-7-methyl-1-azaanthracene (204).⁴³⁸ No mention was made of any attack taking place at C-4. Pyridine and *o*-methylbenzyl chloride gave the quaternary salt 205 which, on heating with a trace of copper, underwent the Ladenburg rearrangement to give a mixture of 206 and 207. The unresolved mixture was passed through a hot (580–590°) tube filled with copper when a mixture of azaanthracenes 208 and 209 was obtained, the latter predominating.⁴³⁹ Apparently 206 and 207 show a smaller tendency



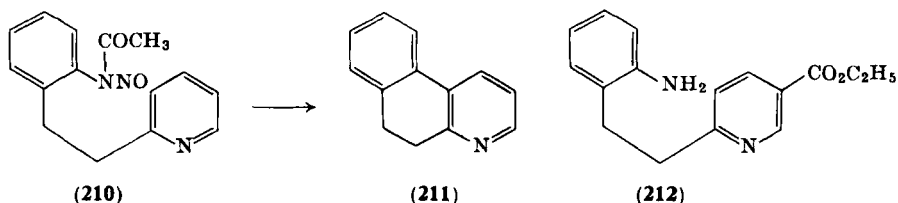
⁴³⁸ O. Nicodemus and W. Berndt, German Patent 514,174 (1925); *Chem. Abstr.* **25**, 2435 (1931).

⁴³⁹ J. von Braun and J. Nelles, *Ber.* **70**, 1760 (1937).



to cyclize than does *o*-tolylphenylmethane. 2-Azaanthracene (209) is said to be formed from xylylpyridine (presumably the 4-*o*-xylyl isomer 207).⁴⁴⁰

Studies on the mechanism of the Pschorr reaction have led to a number of interesting cyclizations onto a pyridine nucleus. Hey and Osbond⁴⁴¹ were the first to carry out such a reaction: 7,8-dihydrobenzo[*f*]quinoline (211) was obtained in 41% yield from the *N*-nitrosoacetanilide (210). The diazonium salt of the amine 212 also underwent cyclization in spite of the presence of a second deactivating



substituent (toward electrophilic attack).⁴⁴² Support for a homolytic mechanism for the copper-catalyzed decomposition of the diazonium salts in aqueous acid solution came from the finding⁴⁴³ that the diazonium salt from 2-amino-*N*-methyl-*N*-(3-pyridyl)aniline (213) is cyclized with copper powder in the cold to a mixture of *ind*-*N*-methyl- δ -carboline (214) (47.5%) and *ind*-*N*-methyl- β -carboline (215)

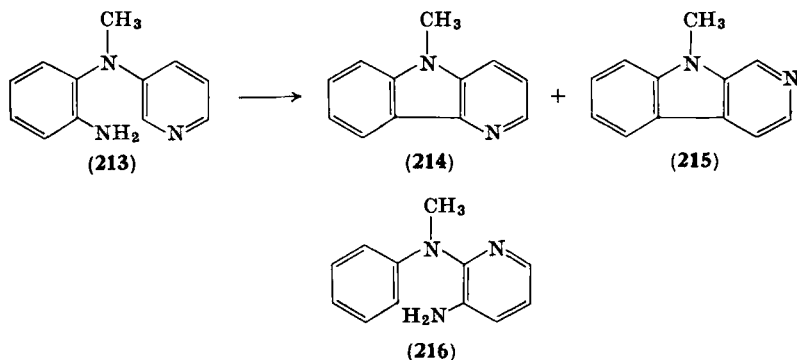
⁴⁴⁰ A. Etienne and J. Robert, *Compt. Rend.* **223**, 331 (1946); *Chem. Abstr.* **41**, 129 (1947).

⁴⁴¹ D. H. Hey and J. M. Osbond, *J. Chem. Soc.* **1949**, 3164.

⁴⁴² H. Plieninger and T. Suehiro, *Ber.* **87**, 882 (1954).

⁴⁴³ R. A. Abramovitch, *Can. J. Chem.* **38**, 2273 (1960).

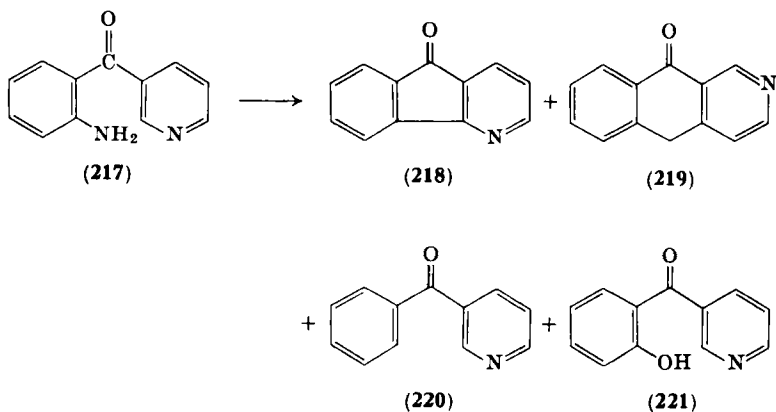
(25.5%), the total yield of cyclized product (73%) being comparable with that obtained (78%) when *N*-(3-amino-2-pyridyl)-*N*-methylaniline (**216**) is ring-closed to the corresponding α -carboline, i.e., a similar cyclization, with similar internuclear separation, onto a benzene ring. When the aqueous acidic solution of the diazonium salt of **213** was boiled, **214** and **215** were again formed, but in lower over-all yield (**214**:**215** = 33:14).⁴⁴³ To avoid possible ambiguity arising from the presence of the activating 3-amino group, the cyclization of the diazonium salt of 3-(2'-aminobenzoyl)pyridine (**217**) was studied under various reaction conditions. With copper powder in aqueous acid



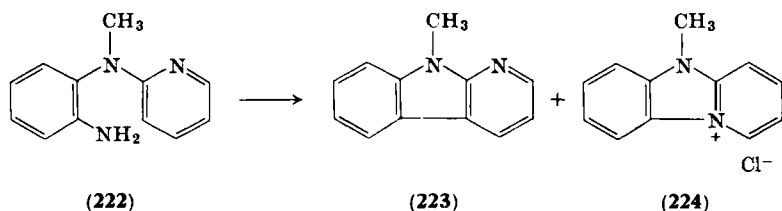
solution, 4-azafluorenone (**218**) (30.3%), 2-azafluorenone (**219**) (19.5%), 3-benzoylpyridine (**220**) (13.0%), and 3-(2'-hydroxyphenyl)pyridine (**221**) (10%) were formed.⁴⁴⁴ When the diazonium salt solution was boiled, **221** was the main product (67%) but some **218** (3.5%) and **219** (2.9%) were still formed. The relatively high yields obtained with copper powder, particularly in the case of **217** which requires cyclization onto a pyridine ring (probably protonated), still further deactivated by a carbonyl group toward electrophilic attack, as well as the fact that both products of attack at the α - and γ -positions of the pyridine ring are obtained, indicate that this is not an electrophilic substitution, but that a homolytic process must be involved. It has been suggested^{444, 445} that the thermal decomposition of the diazonium salts in aqueous acid gives results consistent with the

⁴⁴⁴ R. A. Abramovitch and G. Tertzakian, *Tetrahedron Letters* **1963**, 1511; *Can. J. Chem.* **43**, 940 (1965).

⁴⁴⁵ R. A. Abramovitch, W. A. Hymers, J. B. Rajan, and R. Wilson, *Tetrahedron Letters* 1507 (1963).



formation of a diradical cationic intermediate: this would then behave as a highly "electrophilic" radical. When the diazonium salt from **222** was heated in aqueous acid, a 7% yield of *N*-methyl- α -carboline (**223**) was obtained together with the benzimidazolium salt (**224**) (84%).⁴⁴⁶ This result is again consistent with the participation of a diradical cation intermediate that would prefer to attack the nitrogen atom, which is the center of highest electron-density, but would still be



capable of substituting the π -electron-poor pyridine β -position. The fact that Pschorr cyclizations occur readily onto a pyridine nucleus has been exploited in a synthesis of the benzo[*c*]phenanthridine ring system.⁴⁴⁷ The formation of 5,6-dihydrobenz[*h*]isoquinoline from 4-(2-aminophenylethyl)pyridine has also been reported.⁴⁴⁸

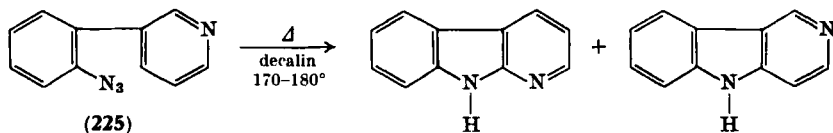
Intramolecular ring closures involving the formation of, and attack by, arylimido intermediates⁴⁴⁹ upon a pyridine ring system have

⁴⁴⁶ R. A. Abramovitch, D. H. Hey, and R. D. Mulley, *J. Chem. Soc.* **1954**, 4263.

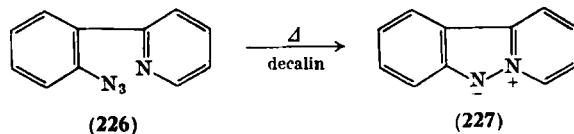
⁴⁴⁷ R. A. Abramovitch and G. Tertzakian, *Can. J. Chem.* **41**, 2265 (1963).

⁴⁴⁸ W. Herz and D. R. K. Murty, *J. Org. Chem.* **26**, 418 (1961).

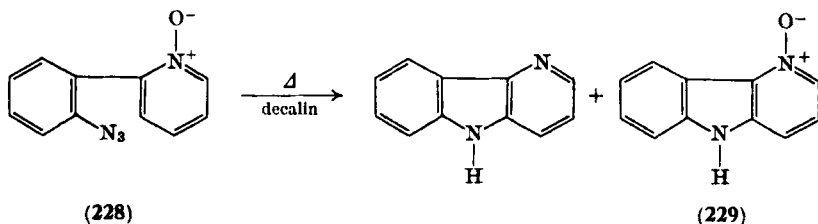
⁴⁴⁹ R. A. Abramovitch and B. A. Davis, *Chem. Rev.* **64**, 149 (1964).



recently been effected. The thermal decomposition of 3-*o*-azidophenylpyridine (225) gave a mixture of α - and γ -carboline (94% yield) in the ratio of 47:23,⁴⁵⁰ ring closure having again involved predominantly (65–70%) the α -position of the pyridine ring. The thermal decomposition of 2-*o*-azidophenylpyridine (226), which does not give rise to any δ -carboline, was thought to give 2-*o*-aminophenylpyridine.⁴⁵⁰ This



has now been shown to be pyrido[1,2-*b*]indazole (227).⁴⁵¹ If the pyridine nitrogen atom is blocked by *N*-oxide formation (228), a mixture of δ -carboline and δ -carboline-*py-N*-oxide (229) could be isolated in low yield.⁴⁵¹ Imido intermediates generated from nitro compounds and ferrous oxalate at 240–300° also attack a pyridine

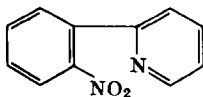


ring. 2-*o*-Nitrophenylpyridine (230) gives 227 but no δ -carboline.^{451, 452} Attempts to block the pyridine nitrogen atom by *N*-oxide or methiodide formation failed due to the prior removal of these blocking groups upon heating with ferrous oxalate.⁴⁵¹ The cyclization of 4-*o*-nitrophenylpyridine to β -carboline by heating with ferrous oxalate presented no difficulties.¹⁶ Similarly, 3-*o*-nitrophenylpyridine gave a

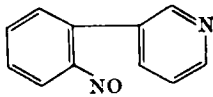
⁴⁵⁰ P. A. S. Smith and J. H. Boyer, *J. Am. Chem. Soc.* **73**, 2626 (1951).

⁴⁵¹ R. A. Abramovitch and K. A. H. Adams, *Can. J. Chem.* **39**, 2516 (1961).

⁴⁵² R. A. Abramovitch, *Chem. Ind. (London)* **1957**, 422.

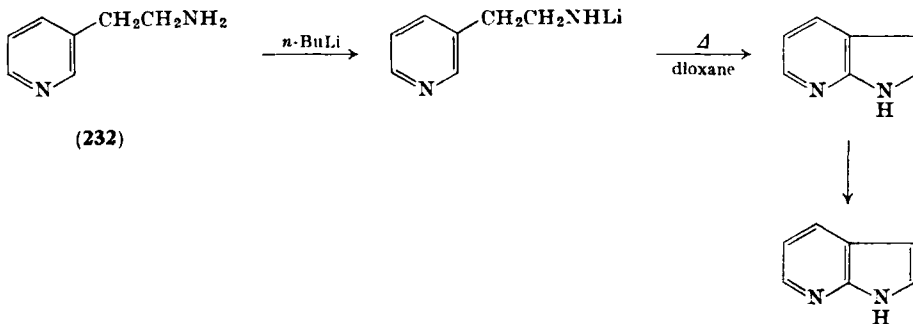


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(231)

mixture of α - and γ -carboline in which the former predominated.⁴⁵³ Deoxygenation of the nitro group in **230** to give the (presumed) imido intermediate which subsequently cyclizes to pyrido[1,2-*b*]indazole (**227**) has also been effected with triethyl phosphite.⁴⁵⁴ The *C*-nitroso compound **231** is deoxygenated by this reagent under much milder conditions and gives a mixture of α - and γ -carboline in which the former again predominates.⁴⁵⁵ Until very recently there were no reports of intramolecular nucleophilic substitutions onto a pyridine ring. These should occur with relative ease and two such cyclizations have now been achieved. When β -(3-pyridyl)ethyl amine (**232**) is treated with *n*-butyllithium and the resulting *N*-lithio salt is heated in dioxane 7-azaindole is formed, presumably by oxidation of the dihydro-compound which results initially (some of the latter has been detected by gas-chromatography).⁴⁵⁶ No product of attack at C-4 has yet been detected. Similarly, the formation of 1,2,3,4-tetrahydro-3-phenyl-1,8-naphthyridine from 2-phenyl-3-(3'-pyridyl) propylamine and sodium has recently been reported.⁴⁵⁷



ACKNOWLEDGMENT

The authors wish to thank Mrs. D. Horning for assistance in the preparation of the manuscript.

⁴⁵³ R. A. Abramovitch, D. E. Horning, and J. G. Saha, Unpubl. results (1964).

⁴⁵⁴ J. I. G. Cadogan and M. Cameron-Wood, *Proc. Chem. Soc.* **1962**, 361.

⁴⁵⁵ P. J. Bunyan and J. I. G. Cadogan, *Proc. Chem. Soc.* **1962**, 78; *J. Chem. Soc.* **1963**, 42.

⁴⁵⁶ R. A. Abramovitch and J. B. Davis, Unpublished results (1965).

⁴⁵⁷ E. M. Hawes and D. G. Wibberley, *J. Chem. Soc.* **1966** (c), 315.

Progress in Pyrazole Chemistry*

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I. Introduction

In the last 20 years the pyrazole ring has attracted much attention, as it has become fairly accessible and shows diverse properties. Besides the traditional interest in pyrazole derivatives which have been the basis of numerous dyes and drugs, a number of pyrazole anesthetics have appeared.^{1,2} Recently it was established that pyrazolines are not only of interest as intermediates in the synthesis of cyclopropanes, but also as effective chemical bleaching agents, and as luminescent and fluorescent substances.³⁻⁸ The ease with which

* Translated by L. C. Johnson, Department of Chemistry, The University, Southampton, England.

¹ H. B. Nisbet, *J. Chem. Soc.* **1938**, 1568.

² N. A. Valyashko and I. T. Depeshko, *Zh. Obshch. Khim.* **23**, 320 (1953).

³ O. Neunhoeffer and D. Rosahl, *Ber.* **86**, 226 (1953).

⁴ E. E. Baroni and K. A. Kovyrzina, *Zh. Obshch. Khim.* **31**, 1641 (1961).

⁵ E. A. Andrishchev, E. E. Baroni, K. A. Kovyrzina, I. M. Rozman, and V. M. Shoniya, *Izv. Akad. Nauk SSSR, Otd. Fiz. Nauk* **22**, 67 (1958).

⁶ Swiss Patent 293,111 (1953); *Ref. Zh. Khim.* **1955**, 19876.

⁷ G. A. Hanson, *Bull. Soc. Chim. Belges* **67**, 707 (1958).

⁸ O. Neunhoeffer, G. Alsdorf, and H. Ulrich, *Ber.* **92**, 252 (1959).

1-phenyl-3-aminopyrazoline is oxidized permits its use in the development of cine-film.⁹ The use of pyrazole derivatives as antioxidants in motor fuels has been discussed. Pyrazoline-1-dithiocarbamates are being studied as interesting complexing agents for the analysis and separation of cations, etc.¹⁰⁻¹¹ As pyrazolines and pyrazolidines have nonaromatic ring structures, the development of their chemistry has been somewhat retarded, but convenient new methods for the synthesis of pyrazoles have recently been evolved and various studies on the pyrazole nucleus have been carried out. As a consequence, certain regularities have been revealed and certain theoretical problems have been formulated in connection with the study of the pyrazole ring.

The use of pyrazole derivatives in medicine is undoubtedly the principal practical application. Certain alkylpyrazoles have shown quite significant bacteriostatic, bacteriocidal, and fungicidal actions.¹²⁻¹⁶ In this respect sulfonamides based on pyrazole are of particular interest, e. g. Orisul (1) which has a prolonged bacteriostatic action *in vivo*.¹⁷⁻²⁰

⁹ G. F. Duffin and J. D. Kendall, *J. Chem. Soc.* **1954**, 408.

¹⁰ A. I. Busev, A. N. Kost, I. I. Grandberg, and V. M. Byr'ko, *Nauchn. Dokl. Vysshei Shkoly, Ser. Khim.* No. 2, **349** (1958).

¹¹ A. I. Busev, V. M. Byr'ko, and I. I. Grandberg, *Vestn. Mosk. Univ., Ser. Khim.* No. 2, **76** (1960).

¹² E. Herrman and J. Gabliks, *Cancer Chemotherapy Rept.* **14**, 85 (1961).

¹³ I. I. Grandberg, S. N. Milovanova, A. N. Kost, and I. T. Nette, *Vestn. Mosk. Univ., Ser. Biol.* No. 3, **27** (1961).

¹⁴ S. Rich and J. G. Horsfall, *Phytopathology* **42**, 457 (1952).

¹⁵ G. L. McNew and N. K. Sundholm, *Phytopathology* **39**, 721 (1949).

¹⁶ E. I. Dvoret'skaya, A. N. Kost, and I. L. Pyrina, *Nauchn. Dokl. Vysshei Shkoly, Ser. Biol.* No. 2, **115** (1958).

¹⁷ M. Guarneri, *Boll. Chim. Farm.* **99**, 259 (1960).

¹⁸ C. Alberti and G. Bregonzio, *Farmaco (Pavia), Ed. Sci.* **16**, 540 (1961).

¹⁹ I. I. Grandberg, "The Study of Pyrazoles," Doctoral Dissertation, Moscow University (1962).

²⁰ C. Alberti, *Farmaco (Pavia), Ed. Sci.* **16**, 557 (1961).

²¹ C. Alberti and C. Tironi, *Farmaco (Pavia), Ed. Sci.* **17**, 443 (1962).

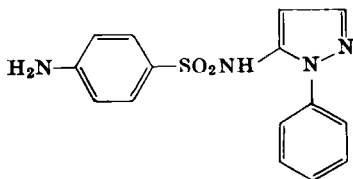
²² C. Alberti and C. Tironi, *Farmaco (Pavia), Ed. Sci.* **17**, 460 (1962).

²³ E. I. Padeiskaya, I. I. Grandberg, G. N. Pershin, A. N. Kost, L. G. Ovseneva, and W.-P. Ting, *Vestn. Mosk. Univ., Ser. Khim.* No. 1, **69** (1963).

²⁴ H. Dorn, K. P. Hilgetag, and G. Hilgetag, *Ber.* **95**, 1372 (1962).

²⁵ K. A. Jensen, *Dansk. Tidsskr. Farm.* **15**, 299 (1941); *Chem. Abstr.* **36**, 5793 (1942).

²⁶ G. W. Raiziss, L. W. Clemence, and M. Freifelder, *J. Am. Chem. Soc.* **63**, 2739 (1941).



(1)

Alkyl- and aryl-pyrazoles themselves have a sharply pronounced sedative action on the central nervous system.^{27,28} Steroidal compounds whose structures include pyrazole rings are of interest as possible psychopharmacological agents.^{29,30} Pyrimidinopyrazoles are being studied in the fight against cancer.³¹

Synthesis of model systems analogous to histamine led to the pharmacologically interesting aminoethylpyrazoles.³²⁻³⁴ Dimethylcarbamates and dialkylphosphates of 5-hydroxypyrazoles have been used practically as choline esterase inhibitors.³⁵⁻⁴¹ Such compounds as Isolan (2), Pyrolan (3), and Pyrazoxon (4), which are too toxic for pharmacology, are used as systemic insecticides. There is evidence that 3,5-dimethylpyrazole has a stimulating action on plants.⁴²

²⁷ G. N. Pershin, N. A. Novitskaya, A. N. Kost, and I. I. Grandberg, *Dokl. Akad. Nauk SSSR* **123**, 200 (1959).

²⁸ Yu. N. Vichlyaev, V. I. Il'inskii, K. S. Raevskii, Yu. M. Batulin, I. I. Grandberg, and A. N. Kost, *Farmakol. i Toksikol.* **25**, 27 (1962).

²⁹ R. O. Clinton, A. J. Manson, F. W. Stonner, H. C. Neumann, R. G. Christiansen, R. L. Clarke, J. H. Ackerman, D. F. Page, J. W. Dean, W. B. Dickinson, and C. Carabateas, *J. Am. Chem. Soc.* **83**, 1478 (1961).

³⁰ R. O. Clinton, A. J. Manson, F. W. Stonner, A. L. Beyler, G. O. Potts, and A. Arnold, *J. Am. Chem. Soc.* **81**, 1513 (1959).

³¹ S. Garattini and V. Palma, *Cancer Chemotherapy Rept.* **13**, 9 (1961); A. Goldin and J. Venditti, *ibid.* **17**, 163 (1962); R. Ihndris, *ibid.* **15**, 67 (1961); J. Scott and L. Foye, *ibid.* **20**, 73 (1962); W. Wilson and N. Bottiglieri, *ibid.* **21**, 137 (1962).

³² R. G. Jones, M. J. Mann, and K. C. McZanghlin, *J. Org. Chem.* **19**, 1428 (1954).

³³ R. G. Jones and M. J. Mann, *J. Am. Chem. Soc.* **75**, 4048 (1953).

³⁴ M. J. S. Dewar, *J. Chem. Soc.* **1944**, 615.

³⁵ R. Wiesmann, R. Gasser, and H. Grob, *Experientia* **7**, 117 (1951).

³⁶ C. C. Roan and S. Maeda, *J. Econ. Entomol.* **47**, 507 (1954).

³⁷ Danish Patent 76,342 (1953); *Ref. Zh. Khim.* **1955**, 4160.

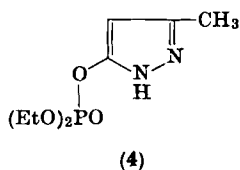
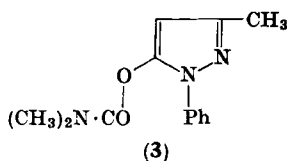
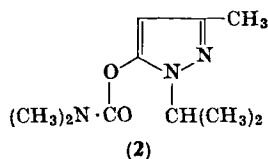
³⁸ G. R. Ferguson and C. C. Alexander, *J. Agr. Food Chem.* **1**, 888 (1953).

³⁹ E. J. Hansens and C. E. Bartley, *J. Econ. Entomol.* **46**, 372 (1953).

⁴⁰ H. Gysin, *Chimia (Aarau)* **8**, 208 (1954).

⁴¹ M. Spindler, *Z. Pflanzenkrankh. Pflanzenschutz* **62**, No. 3, 97 (1955).

⁴² H. E. Thompson, C. P. Swanson, and A. G. Norman, *Botan. Gaz.* **107**, 476 (1946).



In view of the many recent publications concerning pyrazoles it is not surprising that an earlier review on the subject⁴³ has rapidly become outdated.

Pyrazolinones, which are not considered in any detail in this article, have been very fully reviewed in a recent monograph by R. H. and P. Wiley.⁴⁴

II. The General Character of Pyrazoles

A. PHYSICAL AND CHEMICAL PROPERTIES

Pyrazoles are particularly stable compounds with relatively high boiling points. Thus pyrazole itself boils at 187–188° and melts at 70°. It is a colorless compound with a peculiarly penetrating sweetish smell unlike most amines; on account of the persistence of their odor the use of alkylpyrazoles in perfumery has been suggested.⁴⁵ The introduction of substituents in the 3-, 4-, and 5-positions causes the increase in boiling point which is expected with increased molecular weight, but the boiling point falls sharply with substitution in the 1-position. Thus, whereas 3,5-dimethylpyrazole boils at 207°, 1,3,5-trimethylpyrazole boils at 167°. ⁴⁶ Similarly, 1-substituted pyrazoles (even

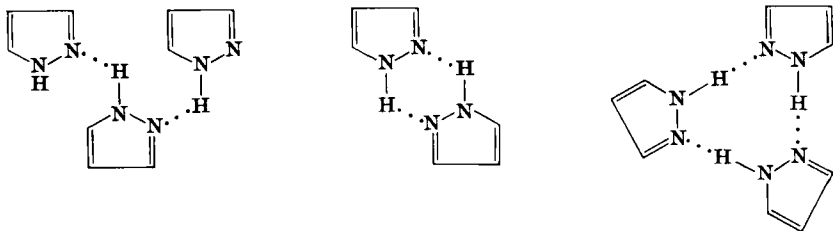
⁴³ T. L. Jacobs, in "Heterocyclic Compounds" (R. C. Elderfield, ed.), Vol. 5, p. 45. Wiley, New York, 1957.

⁴⁴ R. H. Wiley and P. Wiley, "Pyrazolones, Pyrazolidones, and Derivatives," Vol. 20 of "The Chemistry of Heterocyclic Compounds" (A. Weissberger, ed.). Wiley (Interscience), New York, 1964.

⁴⁵ V. N. Belov, N. A. Daev, N. I. Skvortsov, and E. K. Smol'yaninov, *Usp. Khim.* **26**, 96 (1957).

⁴⁶ I. I. Grandberg and A. N. Kost, *Zh. Obshch. Khim.* **30**, 203 (1960).

1-phenylpyrazoles) melt at temperatures significantly lower than the corresponding compounds with free N—H groups. Both of these anomalies are due to the particularly strong association of pyrazoles unsubstituted in position 1, as proved by cryoscopic determinations,⁴⁷⁻⁵⁰ Raman spectral studies,⁵¹ dipole moment measurements,^{50, 52-55} and infrared spectroscopy.⁵⁶⁻⁵⁸ In the gaseous state pyrazole has a normal molecular weight.⁴⁹ It is suggested that the association of pyrazoles may be either linear or into cyclic dimers or trimers^{49, 56}:



These associated forms are most noticeable in the crystalline state; in dilute solution such association is scarcely detectable, as shown by infrared spectroscopy.

Pyrazole and the lower homologs dissolve readily in the majority of organic solvents and in water. The solubilities of pyrazole at 25° in water, benzene, and cyclohexane (expressed as gm/100 gm of solvent)

⁴⁷ N. E. White and M. Kilpatrick, *J. Phys. Chem.* **59**, 1044 (1955).

⁴⁸ H. T. Hayes and L. Hunter, *J. Chem. Soc.* **1941**, 1.

⁴⁹ W. Hückel, J. Datow, and E. Simmersbach, *Z. Physik Chem.* **A186**, 129 (1940).

⁵⁰ W. Hückel and W. Jahnentz, *Ber.* **75B**, 1438 (1942).

⁵¹ G. B. Bonino and R. Manzoni-Ansidei, *Ricerca Sci.* **6**, Part II, 2 (1935); *Chem. Abstr.* **31**, 3388 (1937).

⁵² L. E. Orgel, T. L. Cottrell, W. Dick, and L. E. Sutton, *Trans. Faraday Soc.* **47**, 113 (1951); *Chem. Abstr.* **45**, 7398 (1951).

⁵³ W. Hückel and W. Jahnentz, *Ber.* **74**, 652 (1941).

⁵⁴ K. A. Jensen and A. Friediger, *Kgl. Danske Videnskab. Selskab, Math-Fys. Medd.* **20**, 1 (1943); *Chem. Abstr.* **39**, 2068 (1945).

⁵⁵ W. Hückel, *Ber.* **77**, 810 (1944).

⁵⁶ D. M. W. Anderson, J. L. Duncan, and F. J. C. Rossotti, *J. Chem. Soc.* **1961**, 140.

⁵⁷ P. Mirone and M. Vampiri, *Atti Accad. Nazl. Lincei* **12**, 583 (1952); *Chem. Abstr.* **46**, 9423 (1952).

⁵⁸ I. I. Grandberg, L. I. Gorbacheva, and A. N. Kost, *Zh. Obshch. Khim.* **33**, 513 (1963).

are 130, 18, and 3.⁵⁹ The solubility of 1-methylpyrazole is still higher. In general, however, an increase in molecular weight lowers the solubility in water and raises that in benzene. Pyrazoles are scarcely soluble in petroleum ether, moderately soluble in ether, and dissolve with ease in acetone. Refractive indices of alkylpyrazoles lie in the range 1.46–1.48, and specific gravities lie between 0.89 and 1.02. In order to calculate molecular refractions, von Auwers^{60,61} counted one nitrogen atom as a primary amine and took the value 3.46 for the atomic refraction of the second. For 1-alkylpyrazoles, one nitrogen atom is reckoned as a secondary amine. Thus in the case of 1-phenylpyrazoles an exaltation appears of +0.5 to +2.5 units, which may be due to conjugation. Grandberg and Kost^{62,63} assumed the values 5.871 and 6.245 for the group N—N= in pyrazoles which were respectively unsubstituted and alkyl-substituted in the 1-position. The C=N is included in these group values.

Pyrazoles with free N—H groups are amphoteric though more notably basic than acidic. Thus they form easily hydrolyzed salts with strong acids,⁶⁴ whereas they can give sodium and potassium salts; these too are easily hydrolyzed by water. Electron-withdrawing groups in the ring enhance the acidity of the N—H group.^{65–68} It has been shown that silver salts of such weak acids have structures of type 5 rather than 6,^{68–70} but alkali metal salts have ionic structures. The pK_a of pyrazole itself (2.53)⁷¹ is close to that of 1,2,4-triazole

⁵⁹ H. L. Davis, *J. Am. Chem. Soc.* **63**, 1677 (1941).

⁶⁰ K. von Auwers and W. Kohlhaas, *Ann.* **437**, 36 (1924).

⁶¹ K. von Auwers and W. Ernst, *Z. Physik. Chem.* **122**, 219 (1926).

⁶² I. I. Grandberg and A. N. Kost, *Zh. Obshch. Khim.* **28**, 3071 (1958).

⁶³ I. I. Grandberg and A. N. Kost, *Zh. Obshch. Khim.* **30**, 208 (1960).

⁶⁴ E. Buchner, M. Fritsche, A. Papendieck, and H. Witter, *Ann.* **273**, 214, 232 (1893).

⁶⁵ I. Ambrush, Candidate's Dissertation, Chemistry Faculty, Moscow University (1957).

⁶⁶ I. I. Grandberg and A. N. Kost, *Zh. Obshch. Khim.* **32**, 1556 (1962).

⁶⁷ I. I. Grandberg and A. N. Kost, *Dokl. Akad. Nauk SSSR* **141**, 73 (1961).

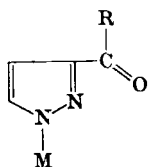
⁶⁸ I. I. Grandberg and A. N. Kost, in "Lecture Summaries for a Conference on the Chemistry of Five-membered Nitrogenous Heterocyclic Compounds," p. 23. Rostov-on-Don, 1962.

⁶⁹ V. G. Vinokurov, V. S. Troitskaya, I. D. Solokhina, and I. I. Grandberg, *Zh. Obshch. Khim.* **33**, 508 (1963).

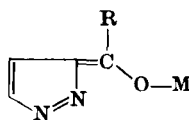
⁷⁰ Yu. N. Sheinker, I. Ambrush, and N. K. Kochetkov, *Dokl. Akad. Nauk SSSR* **123**, 709 (1958).

⁷¹ G. Dedichen, *Ber.* **39**, 1831 (1906).

(2.55),⁷¹ but significantly lower than that of pyridine (5.23) and imidazole (7.03).⁷² The dependence on substitution of the relative basicities of pyrazoles has been studied in detail by Grandberg and Kost.^{66, 67, 73, 74} (See also Wiley and Wiley⁴⁴ and Schoutissen.⁷⁵)

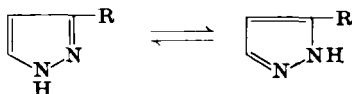


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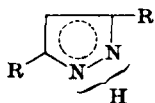


(6)

Pyrazoles which are not substituted on nitrogen exhibit tautomerism,⁷⁶⁻⁸⁰ although von Auwers was unable to separate the tautomeric forms.⁸¹⁻⁸³ The system may be described as one which



includes an aromatic sextet of π -electrons, with the double and single C—C and C—N bonds made equal, and possessing a hydrogen atom in some way connected to both nitrogen atoms simultaneously. It is impossible, however, to represent by a classical structure such a molecule in which a hydrogen atom is connected equally to two



⁷² A. Albert, R. Goldacre, and J. Phillips, *J. Chem. Soc.* **1948**, 2240.

⁷³ I. I. Grandberg, *Zh. Obshch. Khim.* **32**, 3029 (1962).

⁷⁴ I. I. Grandberg and A. N. Kost, *Zh. Obshch. Khim.* **32**, 3025 (1962).

⁷⁵ H. A. J. Schoutissen, *Rec. Trav. Chim.* **54**, 253 (1935).

⁷⁶ K. von Auwers and P. Heimke, *Ann.* **458**, 186 (1927).

⁷⁷ L. Knorr, *Ber.* **28**, 688 (1895).

⁷⁸ L. Knorr, *Ann.* **238**, 137 (1887).

⁷⁹ E. Ott, *Ber.* **62B**, 2685 (1929).

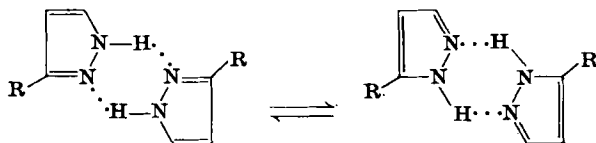
⁸⁰ B. Sjollemma, *Ann.* **279**, 251 (1894).

⁸¹ K. von Auwers and H. Hollmann, *Ber.* **59**, 1282 (1926).

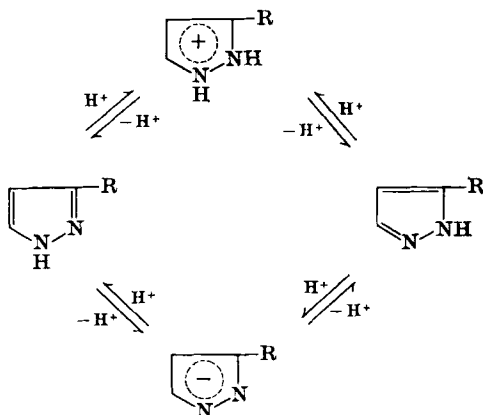
⁸² K. H. Bauer and M. Seyfarth, *Ber.* **63**, 2691 (1930).

⁸³ K. von Auwers and H. Schuhlmann, *Ber.* **59**, 1043 (1926).

nitrogen atoms, from whence it follows that complete symmetry of the monomeric molecule is impossible. The facility of the tautomerism could be explained if all the N—H bonds in the associated structures were assumed to be equivalent.⁸⁴ It is probable that when a strongly



polar group is situated at the 3-position, the molecule predominantly assumes one of the possible structures. This is confirmed indirectly by the molecular refraction of pyrazole carboxylic esters,⁸⁵ and by studies on the N-alkylation of pyrazoles.^{83, 86} It is more correct to explain the tautomerism of pyrazoles by saying that protonation gives the same cation, and alkali gives the same anion,⁸⁷ from either uncharged form of a pyrazole.



An interesting paper was published recently by Wibaut⁸⁸ on the ozonization of pyrazole derivatives. From the ratio of $\text{CH}_3 \cdot \text{CO} \cdot \text{CHO}$ to $\text{CHO} \cdot \text{CHO}$ produced, the author concludes that in the equilibrium

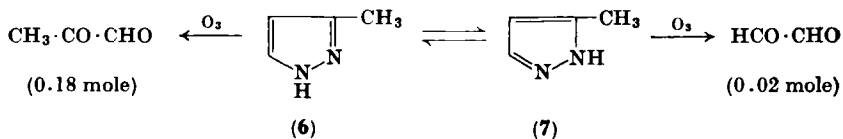
⁸⁴ L. Hunter, *J. Chem. Soc.* **1945**, 806.

⁸⁵ K. von Auwers, *Ann.* **508**, 51 (1933).

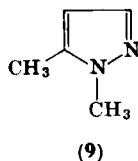
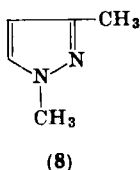
⁸⁶ K. von Auwers and T. Breyhan, *J. Prakt. Chem.* [2] **143**, 259 (1935).

⁸⁷ A. Holleman, "Lehrbuch der organischen Chemie," p. 474. Berlin, Verlag Chemie 1957.

⁸⁸ J. P. Wibaut and J. W. P. Boon, *Helv. Chim. Acta* **44**, 1171 (1961).



between 3- and 5-methylpyrazole ($6 \rightleftharpoons 7$) the former predominates. This result, however, may be explained by a greater reactivity of the former with ozone rather than a preponderance of this form. Substitution on nitrogen prevents tautomerism; thus 1,3- (8) and 1,5-dimethylpyrazole (9) are not identical.⁸¹



B. SPECTROSCOPIC PROPERTIES

The ultraviolet absorption spectra of pyrazoles have been well studied. In a reliable paper by Dal Monte Casoni and co-workers⁸⁹ the spectra of more than 50 pyrazoles are recorded in various solvents and conditions of pH. Alkylpyrazoles show selective absorption with a maximum in the region 210–225 $m\mu$ ($\log \epsilon_{\max}$, 3.5–4.0). The small bathochromic effect of alkyl substituents as a rule does not exceed 2–3 $m\mu$. The maxima for all arylpyrazoles lie between 250–280 $m\mu$ ($\log \epsilon_{\max}$, 3.4–4.2). The introduction of such chromophoric groups as $-\text{NO}_2$, $-\text{CO} \cdot \text{R}$, $-\text{CHO}$, $-\text{COOEt}$ into alkylpyrazoles gives rise to a bathochromic shift of the order of 25–40 $m\mu$.^{89, 90} Ultraviolet spectra of various pyrazoles are available.^{46, 63, 65, 91–97}

⁸⁹ D. Dal Monte Casoni, A. Mangini, and R. Passerini, *Gazz. Chim. Ital.* **86**, 797 (1956).

⁹⁰ I. I. Grandberg, *Zh. Obshch. Khim.* **33**, 518 (1963).

⁹¹ N. K. Kochetkov and I. Ambrush, *Zh. Obshch. Khim.* **27**, 2741 (1957).

⁹² D. S. Noyce, E. Rydel, and B. H. Welkev, *J. Org. Chem.* **20**, 1681 (1955).

⁹³ P. G. Dayton, *Compt. Rend.* **236**, 2515 (1953).

⁹⁴ N. A. Valyashko and V. N. Bliznyukov, *Zh. Obshch. Khim.* **11**, 23 (1941).

⁹⁵ D. M. Burness, *J. Org. Chem.* **21**, 97 (1956).

⁹⁶ A. Mangini and D. Dal Monte Casoni, *Atti Accad. Nazl. Lincei* **13**, 46 (1952).

⁹⁷ D. Dal Monte Casoni, A. Mangini, and R. Passerini, *Bull. Sci. Fac. Chim. Ind. Bologna* **12**, 147 (1954).

Infrared spectra of pyrazoles in the crystalline form and in concentrated solution show an absorption band corresponding to the N—H group in the region $2.7\text{--}3.0\ \mu$ ($3500\text{--}3100\ \text{cm}^{-1}$), the breadth of the band suggesting association.^{57,58,69} An intense band at $6.28\ \mu$ is attributed to C=N, and weak bands at 6.03 and $6.44\ \mu$ to C=C.^{57,98–113} In the latest paper of Zerbi and Alberti¹¹⁴ on the infrared spectra of alkylpyrazoles, an interpretation of the bands in the $650\text{--}3125\ \text{cm}^{-1}$ region is given. Infrared spectra of other pyrazole derivatives are included in a number of papers.^{65,115–118}

From a study of the Raman spectra of pyrazole in solution,⁵¹ it was apparently established that the molecule has a plane of symmetry perpendicular to the plane of the ring, from which it would follow that both nitrogen atoms were equivalent. This should be verified, however, as the author of the paper may have observed the spectrum of the

⁹⁸ E. Brande, *Ann. Repts. Chem. Soc.* **42**, 105 (1945).

⁹⁹ N. A. Rozanov, *Zh. Russ. Fiz.-Khim. Obshch.* **48**, 1227 (1916).

¹⁰⁰ F. L. Scott, *Chimia (Aarau)* **11**, 163 (1957); *Chem. Abstr.* **51**, 17364 (1957).

¹⁰¹ D. Biquard and M. P. Grammaticakis, *Bull. Soc. Chim. France* [5] **8**, 246 (1941).

¹⁰² R. Hüttel and J. Kratzer, *Ber.* **92**, 2014 (1959).

¹⁰³ I. I. Grandberg and A. N. Kost, *Zh. Obshch. Khim.* **29**, 658 (1959).

¹⁰⁴ I. I. Grandberg and A. N. Kost, *Zh. Obshch. Khim.* **29**, 1099 (1959); J. Van Steenis, *Rec. Trav. Chim.* **66**, 29 (1947).

¹⁰⁵ I. I. Grandberg, A. N. Kost, and L. S. Yaguzhinskii, *Zh. Obshch. Khim.* **29**, 2537 (1959).

¹⁰⁶ I. I. Grandberg, A. N. Kost, and D. V. Sibiryakova, *Zh. Obshch. Khim.* **30**, 2920 (1960).

¹⁰⁷ A. P. Terent'ev, I. I. Grandberg, D. V. Sibiryakova, and A. N. Kost, *Zh. Obshch. Khim.* **30**, 2925 (1960).

¹⁰⁸ I. I. Grandberg, A. N. Kost, and N. N. Zheltikova, *Zh. Obshch. Khim.* **30**, 2931 (1960).

¹⁰⁹ I. I. Grandberg, L. G. Vasina, A. S. Volkova, and A. N. Kost, *Zh. Obshch. Khim.* **31**, 1887 (1961).

¹¹⁰ I. I. Grandberg, W.-P. Ting, V. I. Shchegoleva, and A. N. Kost, *Zh. Obshch. Khim.* **31**, 1892 (1961).

¹¹¹ I. I. Grandberg, *Zh. Obshch. Khim.* **31**, 2307 (1961).

¹¹² I. I. Grandberg, W.-P. Ting, and A. N. Kost, *Zh. Obshch. Khim.* **31**, 2311 (1961).

¹¹³ A. Burawoy, *J. Chem. Soc.* **1939**, 1177.

¹¹⁴ G. Zerbi and C. Alberti, *Spectrochim. Acta* **18**, 407 (1962).

¹¹⁵ J. Charrette and P. Teyssie, *Spectrochim. Acta* **15**, 70 (1959).

¹¹⁶ P. Mirone, *Ann. Chim. (Rome)* **46**, 39 (1956); *Chem. Abstr.* **50**, 9154 (1956).

¹¹⁷ W. Ried and F. J. Königstein, *Ann.* **625**, 53 (1959).

¹¹⁸ R. P. Barnes, G. E. Pinkney, and G. McK. Phillips, *J. Am. Chem. Soc.* **76**, 276 (1954).

symmetrical dimer. Certain other structural problems have been tackled by Raman spectral studies.¹¹⁹⁻¹²¹

Grandberg, Tabak, and Kost¹²² have studied the fluorescence in the ultraviolet region of about 300 pyrazole derivatives and recorded how this depends on structure. Papers by Vinokurov^{69, 123, 123a} are concerned with the possible tautomerism of hydroxy-, acyl-, and amino-pyrazoles. (See also references^{123b} and^{123c} concerning this problem.) Huckel^{50, 53, 55} observed that the dipole moment of pyrazole was quite small (2.64 D), which is probably due to strong association of the molecules. (On dipole moment of pyrazoles, see also reference 123d.) He also measured the heat of solution viscosity, specific conductivity, and surface tension of pyrazole⁴⁹; concerning the surface tension of pyrazole see also Huckel and Jahnentz.⁵⁰

The work of Parsons^{124, 125} deals with the structure of the crystal lattices of pyrazole carboxylic esters. Comment on the polymorphism of pyrazoles is given by Weygand,¹²⁶ and data concerning the orientation of 3,5-dimethylpyrazole adsorbed on montmorillonite are given by Greene-Kelly.¹²⁷ Calculations of the electron distribution density for all carbon and nitrogen atoms, of bond orders, and of localization energies, have been recorded by Bown¹²⁸ and Basu¹²⁹ for pyrazoles with electrophilic and nucleophilic substituents. Although the non-equivalence of the 3/5- and the 4-positions is agreed, some of the

¹¹⁹ K. W. I. Kohlrausch and R. Seka, *Ber.* **71**, 1563 (1938).

¹²⁰ G. B. Bonino and R. Manzoni-Asidei, *Mem. Accad. Sci. Inst. Bologna, Classe Sci. Fis.* [9] **1**, 7 (1934); *Chem. Abstr.* **29**, 1712 (1935).

¹²¹ R. Manzoni-Asidei and L. Caoalloro, *Ricerca Sci.* **7**, Part II, 1 (1936); *Chem. Abstr.* **32**, 4879 (1938).

¹²² I. I. Grandberg, S. V. Tabak, and A. N. Kost, *Zh. Obshch. Khim.* **33**, 527 (1963).

¹²³ I. I. Grandberg, V. G. Vinokurov, V. S. Troitskaya, and G. I. Sharova, *Zh. Obshch. Khim.* **32**, 3417 (1962).

^{123a} V. G. Vinokurov, V. S. Troitskaya, and I. I. Grandberg, *Zh. Obshch. Khim.* **34**, 654 (1964).

^{123b} A. R. Katritzky and F. W. Maine, *Tetrahedron* **20**, 315 (1964).

^{123c} A. R. Katritzky and F. W. Maine, *Tetrahedron* **20**, 299 (1964).

^{123d} S. A. Giller, I. B. Mazhejka, and I. I. Grandberg, *Khim. geterocycl. Soedyn.*, **1**, 103, 107 (1965).

¹²⁴ J. Parsons, *Acta Cryst.* **6**, 367 (1953); *Chem. Abstr.* **47**, 8457 (1954).

¹²⁵ J. Parsons and W. C. McCrone, *Anal. Chem.* **26**, 247 (1954); *Chem. Abstr.* **48**, 4925 (1954).

¹²⁶ C. Weygand, *Ber.* **62B**, 2603 (1929).

¹²⁷ R. Greene-Kelly, *Trans. Faraday Soc.* **51**, 412 (1955).

¹²⁸ R. Bown, *Australian J. Chem.* **8**, 100 (1955).

¹²⁹ S. Basu, *Proc. Natl. Inst. Sci. India* **21A**, 173 (1955).

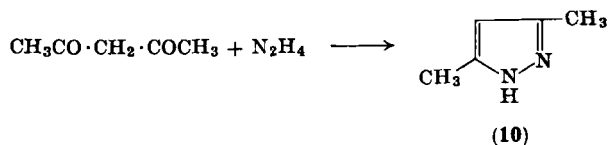
experimental data in these papers are conflicting. By molecular orbital calculations, Orgel⁵² has predicted that the maximum electron density occurs at position 4 in the ring, in agreement with the results of electrophilic substitution experiments.

The nuclear magnetic resonance spectra of certain pyrazoles have been studied.¹³⁰ Somewhat paradoxically the hydrogen atoms in positions 3 and 5 of N-substituted pyrazoles have the same chemical shifts, though they are by no means identical chemically. (On NMR spectra of pyrazoles see also references 130a, 130b, and 130c.) It has been shown that 1,3-dialkylpyrazoles are stronger bases than the corresponding 1,5-isomers.^{19,44} For other physical properties, see references 131–133.

III. The Synthesis of Pyrazoles

A. SYNTHESIS FROM HYDRAZINE AND ITS DERIVATIVES

One of the most important methods of pyrazole synthesis involves the reaction of 1,3-diketones with hydrazine derivatives. The method has wide scope, especially considering that the diketones may be replaced by acetals, hemiacetals, chlorovinyl ketones, tetrahalides, etc. Most accessible by this path is 3,5-dimethylpyrazole (10), obtained in 85% yield from acetylacetone and hydrazine hydrate.^{134–136}



¹³⁰ L. Fowden, F. F. Noe, J. H. Ridd, and R. F. M. White, *Proc. Chem. Soc.* **1959**, 131.

^{130a} I. L. Finar and E. Mooney, *Spectrochim. Acta* **20**, 1269 (1964).

^{130b} J. K. Williams, *J. Org. Chem.* **22**, 1377 (1964).

^{130c} V. J. Bistrov, I. I. Grandberg, and J. I. Sharova, *Zh. Obshch. Khim.* **35**, 293 (1965).

¹³¹ H. Ehrlich, *Acta Cryst.* **13**, 946 (1960).

¹³² D. M. W. Anderson, J. L. Duncan, and J. J. C. Rossotti, *J. Chem. Soc.* **1961**, 140.

¹³³ J. D. Loudon, "Chemistry of Carbon Compounds" (E. H. Rodd, ed.), Vol. 4, Part A, p. 254. Elsevier, Amsterdam, 1957.

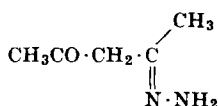
^{133a} S. Tabak, I. I. Grandberg, and A. N. Kost, *J. Chromatog.* **17**, 520 (1965).

¹³⁴ G. D. Rosengarten, *Ann.* **279**, 237 (1894).

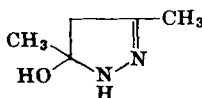
¹³⁵ R. Rothenburg, *Ber.* **27**, 1097 (1894).

¹³⁶ G. K. Hughes, F. Lions, J. J. Maunsell, and T. Wilkinson, *J. Proc. Roy. Soc. N.S. Wales* **71**, 406 (1938).

Practically all linear 1,3-diketones¹³⁷⁻¹⁴² give the corresponding pyrazoles with hydrazine^{104,143} and its derivatives.¹⁴⁴⁻¹⁴⁹ The reaction of aliphatic diketones should be moderated by dilution, cooling, or the addition of acid.¹³⁷ Since pyrazole rings are stable, severe conditions may be used in their preparation where necessary. For details of the hydrazine/acetylacetone reaction see Wiley and Hexner.¹⁵⁰ Evidently the reaction proceeds via the formation of the monohydrazone (11)¹⁵¹ which, when aryl-substituted, is less reactive and may be isolated.^{83, 152-159} (However, see reference 159a.) It is not known if the monohydrazone are cyclic (12) or not, but they are



(11)



(12)

- ¹³⁷ V. V. Korshak, E. S. Krongaus, A. M. Berlin, and P. N. Gribkova, *Dokl. Akad. Nauk SSSR* **149**, 602 (1963).
- ¹³⁸ L. I. Smith and E. R. Rogier, *J. Am. Chem. Soc.* **73**, 3831 (1951).
- ¹³⁹ G. W. Cannon and H. L. Whidden, *J. Org. Chem.* **17**, 685 (1952).
- ¹⁴⁰ L. I. Smith and V. A. Engelhardt, *J. Am. Chem. Soc.* **71**, 2671 (1949).
- ¹⁴¹ C. D. Hurd and C. D. Kelso, *J. Am. Chem. Soc.* **62**, 2184 (1940).
- ¹⁴² B. Eistert and R. Wessendorf, *Ber.* **94**, 2590 (1961).
- ¹⁴³ H. H. Szmant and D. A. Irwin, *J. Am. Chem. Soc.* **78**, 4386 (1956).
- ¹⁴⁴ S. S. Joshi and J. R. Gambhir, *J. Am. Chem. Soc.* **78**, 2222 (1956).
- ¹⁴⁵ H. Schmid and D. Bolleter, *Helv. Chim. Acta* **33**, 917 (1950).
- ¹⁴⁶ P. J. Drumm, *Proc. Roy. Irish Acad.* **40B**, 106 (1931); *Chem. Abstr.* **26**, 452 (1932).
- ¹⁴⁷ J. Wislicenus, *Ann.* **308**, 254 (1899).
- ¹⁴⁸ M. Renard and A. Maquinay, *Bull. Soc. Chim. Belges* **55**, 98 (1946); *Chem. Abstr.* **41**, 4104 (1947).
- ¹⁴⁹ A. Pinter and R. Robinson, *J. Chem. Soc.* **1955**, 334.
- ¹⁵⁰ R. H. Wiley and P. E. Hexner, *Org. Syn.* **31**, 43 (1951).
- ¹⁵¹ N. A. Domnin, S.-K. Van, and N. S. Glebovskaya, *Zh. Obshch. Khim.* **27**, 1512 (1957).
- ¹⁵² K. von Auwers and W. Schmidt, *Ber.* **58**, 528 (1925).
- ¹⁵³ K. von Auwers and E. Cauer, *J. Prakt. Chem.* [2] **126**, 146 (1930).
- ¹⁵⁴ W. Borsche and H. Hahn, *Ann.* **537**, 219 (1939).
- ¹⁵⁵ L. Panizzi, *Gazz. Chim. Ital.* **77**, 283 (1947).
- ¹⁵⁶ K. von Auwers and K. Dietrich, *J. Prakt. Chem.* [2] **139**, 65 (1934).
- ¹⁵⁷ C. F. Woodward and R. C. Fuson, *J. Am. Chem. Soc.* **55**, 3472 (1933).
- ¹⁵⁸ H. Couturier, *Compt. Rend.* **150**, 928 (1910).
- ¹⁵⁹ K. von Auwers and H. Mauss, *Ann.* **452**, 182 (1927).
- ^{159a} S. Veibel, A. K. Dramon, and I. G. Andersen, *Z. Anal. Chem.* **200**, 439 (1964).

converted to pyrazoles by the action of heat or acids.^{134, 152, 155, 159-162}

Bis-hydrazones, formed when the hydrazine is in excess, readily give pyrazoles on heating.^{155, 159-161, 163-165} The hydrazine component may be alkyl-substituted,¹⁶⁶ or aryl-substituted,^{61, 104, 167-174} and even 2,4-dinitrophenylhydrazine takes part in the reaction.¹⁷⁵⁻¹⁸¹ Sulfanilhydrazide,¹⁸² semicarbazide,¹⁸³⁻¹⁸⁶ and various acyl hydrazines^{153, 156, 187-190} and aminoguanidine^{190a-190g} have all been used

¹⁶⁰ K. von Auwers and B. Ottens, *Ber.* **58**, 2072 (1925).

¹⁶¹ A. Michael and J. Ross, *J. Am. Chem. Soc.* **53**, 2394 (1931).

¹⁶² C. Barat, *J. Indian Chem. Soc.* **8**, 801 (1931).

¹⁶³ O. Wallach, *Ann.* **329**, 131 (1903).

¹⁶⁴ H. Rupe and A. Huber, *Helv. Chim. Acta* **10**, 846 (1927).

¹⁶⁵ C. F. Huebner and K. P. Link, *J. Am. Chem. Soc.* **72**, 4812 (1950).

¹⁶⁶ F. L. Scott, A. Ahearne, and J. Reilly, *Rec. Trav. Chim.* **76**, 190 (1957).

¹⁶⁷ B. Umapasama, *J. Indian Chem. Soc.* **8**, 119 (1931).

¹⁶⁸ H. Keller and H. von Halban, *Helv. Chim. Acta* **27**, 1253 (1944).

¹⁶⁹ H. A. J. Schoutissen, *Rec. Trav. Chim.* **53**, 561 (1934).

¹⁷⁰ K. von Auwers and R. Hugel, *J. Prakt. Chem.* [2] **143**, 157 (1935).

¹⁷¹ N. H. Cromwell and G. Mercer, *J. Am. Chem. Soc.* **79**, 3819 (1957).

¹⁷² H. O. House and D. J. Reif, *J. Am. Chem. Soc.* **77**, 6525 (1955).

¹⁷³ T. Ajello and S. Giambrone, *Bull. Sci. Fac. Chim. Ind. Bologna* **11**, 93 (1953).

¹⁷⁴ H. Schmidt and F. Meijer, *Helv. Chim. Acta* **31**, 748 (1948).

¹⁷⁵ R. E. Foster, A. W. Larcher, R. D. Lipscomb, and B. C. McCusick, *J. Am. Chem. Soc.* **78**, 5606 (1956).

¹⁷⁶ L. Knorr, *Ber.* **16**, 2593 (1883).

¹⁷⁷ W. J. Croxall and J. O. Van Hook, *J. Am. Chem. Soc.* **71**, 2422 (1949).

¹⁷⁸ W. Borsche and W. Ried, *Ann.* **554**, 282 (1943).

¹⁷⁹ O. L. Brady, *J. Chem. Soc.* **1931**, 756.

¹⁸⁰ U.S. Patent 2,527,533 (1950); *Chem. Abstr.* **45**, 1622 (1951).

¹⁸¹ A. L. Lehninger, *J. Biol. Chem.* **153**, 561 (1944).

¹⁸² K. A. Jensen and O. R. Hansen, *Acta Chem. Scand.* **6**, 195 (1952).

¹⁸³ T. Mkryan and N. Papazyan, *Dokl. Akad. Nauk Arm. SSR* **16**, 103 (1953).

¹⁸⁴ I. M. Heilbron, D. H. Hey, and A. Lowe, *J. Chem. Soc.* **1934**, 1311.

¹⁸⁵ T. Posner, *Ber.* **34**, 3983 (1901).

¹⁸⁶ C. D. Hurd and C. D. Kelso, *J. Am. Chem. Soc.* **62**, 2184 (1940).

¹⁸⁷ W. Ried and A. Meyer, *Ber.* **90**, 2841 (1957).

¹⁸⁸ W. Ried and B. Schleimer, *Angew. Chem.* **70**, 164 (1958).

¹⁸⁹ H. Strain, *J. Am. Chem. Soc.* **57**, 758 (1935).

¹⁹⁰ H. von Euler and B. Häggglund, *Arkiv Kemi, Mineral., Geol.* **A19**, 10 (1945); *Chem. Abstr.* **41**, 1660 (1947).

^{190a} S. Levy and F. C. Witte, *Ann.* **252**, 343 (1889).

^{190b} S. C. De and P. C. Rakshit, *J. Indian Chem. Soc.* **13**, 509 (1936).

^{190c} F. L. Scott, C. M. B. Murphy, and J. Reilly, *Nature* **167**, 1037 (1951).

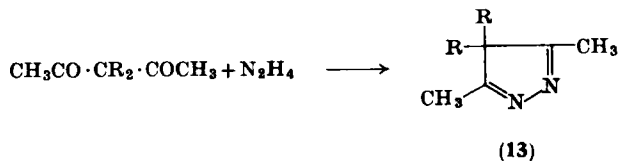
^{190d} R. A. Henry and G. B. L. Smith, *J. Am. Chem. Soc.* **74**, 278 (1952).

^{190e} F. L. Scott and J. Reilly, *Chem. Ind. (London)* **1952**, 907.

^{190f} F. L. Scott, M. T. Kennedy, and J. Reilly, *J. Am. Chem. Soc.* **75**, 1294 (1953).

^{190g} F. L. Scott, M. Cashman, and J. Reilly, *J. Am. Chem. Soc.* **75**, 1510 (1953).

successfully in this synthesis. Hydrolysis of the *N*-acyl residue in the various products is easily accomplished. Steric hindrance of the reaction is not marked,¹⁵⁷ although cyclic diketones such as cyclohexane-1,3-dione and indane-1,3-dione give only hydrazones and azines.¹⁹¹ Dialkylacetylacetones react energetically with hydrazine hydrate to give 4*H*-pyrazoles (13).^{192, 193} The reaction is not impeded by the



presence in the 1,3-diketone molecule of such groups as $-\text{NO}$,¹⁹⁴⁻¹⁹⁹ $-\text{NO}_2$,²⁰⁰ $-\text{N}=\text{N}-\text{Ph}$,²⁰¹⁻²⁰⁵ and $-\text{CH}_2 \cdot \text{COOH}$.²⁰⁶ Diketone carboxylic acids and esters, depending on the nature of the reagent and the reaction conditions, give either pyrazoles or pyrazolinones as follows²⁰⁷⁻²¹⁸:

¹⁹¹ H. Reisengger, *Ber.* **16**, 661 (1883).

¹⁹² L. Knorr and B. Oettinger, *Ann.* **279**, 247 (1894).

¹⁹³ K. von Auwers and E. Bergmann, *Ann.* **472**, 287 (1929).

¹⁹⁴ J. Reilly and D. MacSweeney, *Proc. Roy. Irish Acad.* **39B**, 497 (1930).

¹⁹⁵ L. Wolff, *Ann.* **325**, 129 (1902).

¹⁹⁶ T. Kosuge and H. Okeda, *J. Biochem. (Tokyo)* **41**, 183 (1954).

¹⁹⁷ N. K. Sundholm, U.S. Patent 2,510,724 (1950).

¹⁹⁸ M. Ruccia, *Ann. Chim. (Rome)* **49**, 720 (1959).

¹⁹⁹ W. Freemann and R. Slack, British Patent 783,706 (1957).

²⁰⁰ H. B. Hill and I. Torrey, *Am. Chem. J.* **22**, 89 (1899).

²⁰¹ H. von Pechmann and K. Jenisch, *Ber.* **24**, 3255 (1891).

²⁰² T. Lincke and O. Kegel, *Ber.* **22**, 1478 (1889).

²⁰³ C. Beyer and L. Claisen, *Ber.* **21**, 1697 (1888).

²⁰⁴ L. Claisen, *Ber.* **36**, 3664 (1903).

²⁰⁵ A. K. Macbeth, *J. Chem. Soc.* **123**, 1122 (1923).

²⁰⁶ R. Lukeš and K. Syhora, *Chem. Listy* **48**, 560 (1954).

²⁰⁷ L. Knorr and A. Blank, *Ber.* **18A**, 311 (1885).

²⁰⁸ L. Knorr, *Ann.* **279**, 237 (1894).

²⁰⁹ F. Seidel, *Ber.* **65**, 1205 (1932).

²¹⁰ F. Seidel, W. Thier, A. Uber, and J. Dittmer, *Ber.* **68B**, 1913 (1932).

²¹¹ S. C. De and D. N. Dutt, *J. Indian Chem. Soc.* **7**, 473 (1930).

²¹² L. Bouveault and A. Bongert, *Bull. Soc. Chim. France* [3] **27**, 1095, 1100 (1902).

²¹³ W. J. Barri and I. L. Finar, *J. Chem. Soc.* **1954**, 138.

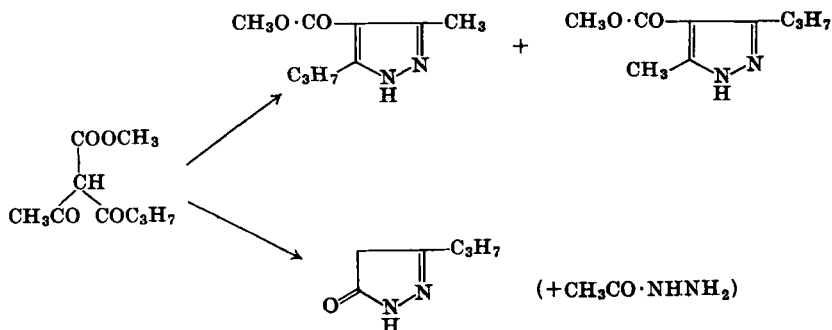
²¹⁴ D. Libermann, *Bull. Soc. Chim. France* **1950**, 1217; *Chem. Abstr.* **45**, 7964 (1951).

²¹⁵ R. Richter, *Helv. Chim. Acta* **35**, 478 (1952).

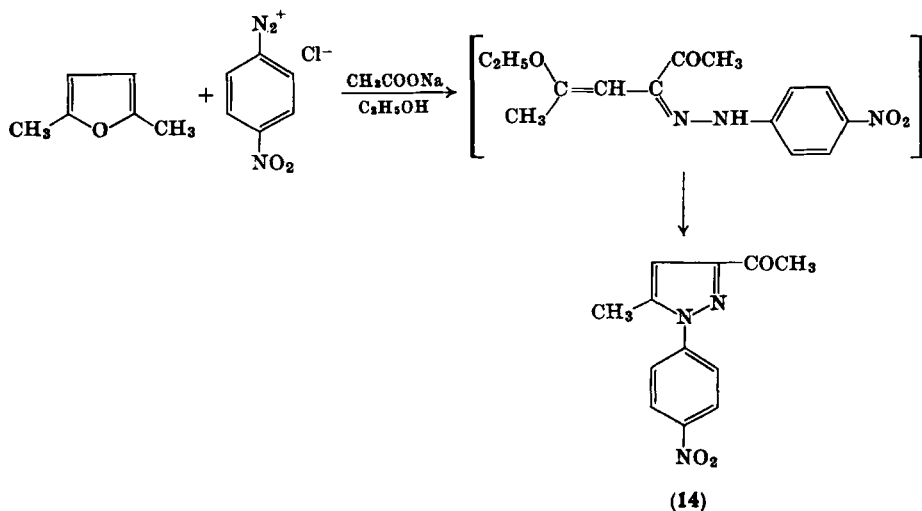
²¹⁶ U. E. Eisner, J. A. Elvidge, and R. P. Linstead, *J. Chem. Soc.* **1951**, 1501.

²¹⁷ M. J. S. Dewar and F. E. King, *J. Chem. Soc.* **1945**, 114.

²¹⁸ C. A. Rojahn, *Ber.* **59**, 607 (1926).



A series of pyrazoles was obtained by azo-coupling of acetoacetic ester derivatives and cyclization of the arylhydrazones formed.²¹⁹⁻²²⁹ Probably a similar type of reaction occurs with *p*-nitrophenyldiazo-



²¹⁹ I. L. Finar, *J. Chem. Soc.* **1955**, 1205.

²²⁰ A. Bischler, *Ber.* **25**, 3143 (1892).

²²¹ A. Bischler and W. Oser, *Ber.* **26**, 1881 (1893).

²²² H. Staudinger, *Helv. Chim. Acta* **4**, 239 (1921).

²²³ C. Bülow, *Ber.* **33**, 3266 (1900).

²²⁴ C. Bülow and K. Baur, *Ber.* **58**, 1926 (1925).

²²⁵ E. C. Taylor, J. W. Barton, and T. S. Osdene, *J. Am. Chem. Soc.* **80**, 421 (1958).

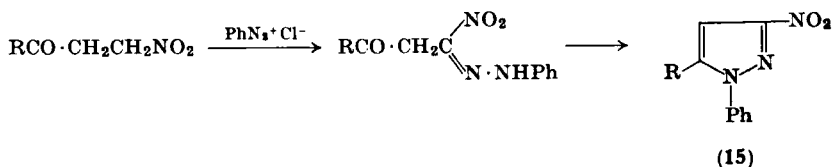
²²⁶ V. Meyer, *Ber.* **21**, 11 (1888).

²²⁷ C. Bülow and A. Schlesinger, *Ber.* **32**, 2880 (1899).

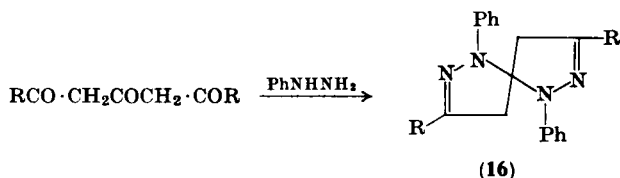
²²⁸ C. Bülow and A. Schlesinger, *Ber.* **33**, 3362 (1900).

²²⁹ R. H. Eastman and F. L. Detert, *J. Am. Chem. Soc.* **70**, 962 (1948).

nium chloride and 2,5-dimethylfuran since a pyrazole (14) is formed.²²⁹ The synthesis of 3-nitropyrazoles (15) by Fusco²³⁰ is a similar type of reaction; see also Lund²³¹ and Clemo.²³² Spirobispyrazolines (16) are



formed from 1,3-triketones and phenylhydrazine.^{207, 233-235} Syntheses of polypyrazoles from tetraketones see references 235a and 235b.



Enol ethers of 1,3-diketones react in weakly acidic media as the diketones themselves.²³⁶ The synthesis of pyrazoles with various heterocyclic substituents has been liberally covered in the literature.²³⁷⁻²⁵⁹

²³⁰ R. Fusco and S. Rossi, *Rend. Ist. Lombardo Sci. Lettere, Sect. A* **93**, 334 (1959).

²³¹ H. Lund, *J. Chem. Soc.* **1933**, 686.

²³² G. R. Clemo and T. Holmes, *J. Chem. Soc.* **1934**, 1739.

²³³ L. Knorr, *Ber.* **16**, 2597 (1883).

²³⁴ L. Knorr, *Ber.* **17**, 2032 (1884).

²³⁵ L. Knorr and F. Jödicke, *Ber.* **18**, 2256 (1885).

^{235a} V. V. Korshak, E. S. Krongaus, and A. M. Berlin, *Dokl. Akad. Nauk SSSR* **152**, 1108 (1963).

^{235b} V. V. Korshak, E. S. Krongaus, A. M. Berlin, and T. Ya. Smirnova, *Visokomol. Soedin.* **6**, 1195 (1964).

²³⁶ J. Pascual and F. Serratosa, *Ber.* **85**, 686 (1952).

²³⁷ L. Panizzi and E. Monti, *Gazz. Chim. Ital.* **77**, 556 (1947).

²³⁸ R. Kuhn and K. Henkel, *Ann.* **549**, 279 (1941).

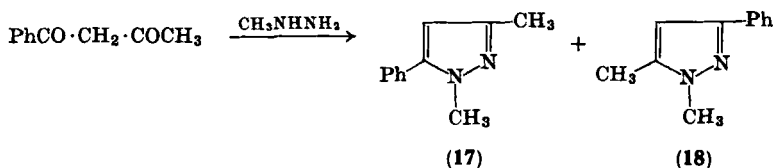
²³⁹ A. A. Ponomarev and L. V. Cherkasova, in "Lecture Summaries for a Conference on the Chemistry of Five-membered Nitrogenous Heterocyclic Compounds," p. 25. Rostov-on-Don, 1962.

²⁴⁰ N. K. Kochetkov, E. B. Nifant'ev, and L. V. Nifant'eva, *Zh. Obshch. Khim.* **30**, 241 (1960).

²⁴¹ H. Veldstra and P. W. Wiardi, *Rec. Trav. Chim.* **61**, 627 (1942).

²⁴² A. Treibs and K. Michl, *Ann.* **577**, 129 (1952).

The principal drawback of the method is that unsymmetrical 1,3-diketones generally give two products (**17**, **18**) (see, for example, Finar and Hurlock).²⁶⁰



In a number of early papers only one isomer was said to be formed,^{146, 159, 261} but this conclusion was often incorrect and due to inadequate separation procedures. Even keto aldehydes (hydroxy-methylene ketones) tend to give two products in spite of the considerable difference between the carbonyl groups^{159, 262}; here again the earlier papers were at fault.^{263, 264} The reactions of hydroxy-methylene acetophenone, which is particularly accessible, with

²⁴³ British Patent 791,688 (1958); *Chem. Abstr.* **52**, 15595 (1958).

²⁴⁴ G. B. Crippa and R. Caracci, *Gazz. Chim. Ital.* **71**, 574 (1941).

²⁴⁵ F. L. Scott, D. G. O'Donovan, and J. Reilly, *J. Appl. Chem. (London)* **2**, 368 (1952).

²⁴⁶ G. Salvatori, *Gazz. Chim. Ital.* **21**, 268 (1891).

²⁴⁷ H. King, *J. Chem. Soc.* **1932**, 2768.

²⁴⁸ G. A. C. Gough and H. King, *J. Chem. Soc.* **1933**, 350.

²⁴⁹ N. K. Sadovaya, "Substitution Reactions in the Selenophen Series," Candidate's Dissertation, Moscow University (1962).

²⁵⁰ G. A. C. Gough and H. King, *J. Chem. Soc.* **1931**, 2968.

²⁵¹ C. Musante, *Gazz. Chim. Ital.* **71**, 172 (1941).

²⁵² T. N. Ghosh and D. Das-Gupta, *J. Indian Chem. Soc.* **16**, 63 (1939); *Chem. Abstr.* **33**, 5846 (1939).

²⁵³ C. Musante, *Gazz. Chim. Ital.* **70**, 685 (1940).

²⁵⁴ J. Weijlard, *J. Am. Chem. Soc.* **67**, 1031 (1945).

²⁵⁵ L. Fabbri, *Farmaco (Pavia)*, *Ed. Sci.* **9**, 603 (1954); *Chem. Abstr.* **49**, 14763 (1955).

²⁵⁶ R. C. Linares, M. D. Bayes, and J. P. Cardona, *Publ. Inst. Quim. "Alonso Barba" (Madrid)* **4**, 310 (1950); *Chem. Abstr.* **46**, 8082 (1952).

²⁵⁷ C. Musante and R. Berretti, *Gazz. Chim. Ital.* **79**, 683 (1950).

²⁵⁸ F. Weygand and K. Henkel, *Ber.* **76**, 818 (1943).

²⁵⁹ E. Fischer and C. Bülow, *Ber.* **18**, 2131 (1885).

²⁶⁰ I. L. Finar and R. J. Hurlock, *J. Chem. Soc.* **1958**, 3259.

²⁶¹ K. von Auwers and F. Dersch, *Ann.* **462**, 104 (1928).

²⁶² T. Kosuge, Japanese Patent 5,882 (1954); *Chem. Abstr.* **50**, 7145 (1956).

²⁶³ L. Claisen and N. Stylos, *Ber.* **21**, 1147 (1888).

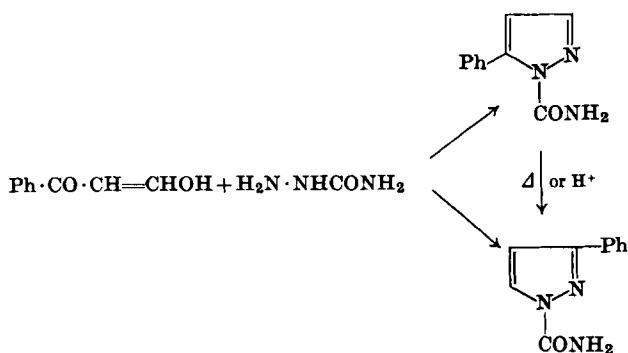
²⁶⁴ L. Claisen and P. Roosen, *Ann.* **278**, 276 (1893).

various hydrazines have been studied in detail^{152, 156, 159, 237, 265, 266}; other hydroxymethylene ketones feature in a number of other papers.^{60, 81, 164, 267-290} Besides hydroxymethylene ketones, their enol-ethers, benzoates, and ethoxycarbonyl derivatives also react smoothly with hydrazines.^{159, 291} It should be noted that the majority of 1,3-dicarbonyl compounds are obtained by Claisen condensations, which for diketones and keto aldehydes give mixtures of products.^{292, 293} It is not always possible to be sure that they are individual substances. According to Finar²⁹⁴ the structure of these substances may be studied via their conversion to pyrazoles.^{294a} It was

- ²⁶⁵ K. von Auwers and H. Mauss, *J. Prakt. Chem.* [2] **117**, 311 (1927).
²⁶⁶ K. von Auwers and H. Wunderling, *Ber.* **67**, 644 (1934).
²⁶⁷ I. K. Korobitsyna, Yu. K. Yur'ev, Ch.-L. Yin, A. F. Davydova, and N. N. Gaidamovich, *Zh. Obshch. Khim.* **31**, 3921 (1961).
²⁶⁸ L. Panizzi and O. Benuti, *Gazz. Chim. Ital.* **76**, 66 (1946).
²⁶⁹ T. Kosuge and H. Isogai, *J. Pharm. Soc. Japan* **73**, 435 (1953); *Chem. Abstr.* **48**, 5104 (1954).
²⁷⁰ E. Profft, F. Runge, and H. Blanke, *J. Prakt. Chem.* [4] **1**, 110 (1955).
²⁷¹ A. Dornow and K. Peterlein, *Ber.* **82**, 257 (1949).
²⁷² C. A. Grob and K. Camenisch, *Helv. Chim. Acta* **36**, 37 (1953).
²⁷³ D. E. Fanta and R. A. Stein, *Chem. Rev.* **60**, 261 (1960).
²⁷⁴ W. Franke and R. Kraft, *Ber.* **86**, 797 (1953).
²⁷⁵ T. Kosuge, *J. Pharm. Soc. Japan* **72**, 1227 (1952).
²⁷⁶ F. B. Dains and R. N. Harger, *J. Am. Chem. Soc.* **40**, 562 (1918).
²⁷⁷ F. B. Dains and W. S. Long, *J. Am. Chem. Soc.* **43**, 1200 (1921).
²⁷⁸ L. Panizzi, *Gazz. Chim. Ital.* **73**, 13 (1943).
²⁷⁹ E. Weitz and A. Scheffer, *Ber.* **54**, 2344 (1921).
²⁸⁰ K. von Auwers and K. Bähr, *J. Prakt. Chem.* [2] **116**, 65 (1927).
²⁸¹ K. von Auwers and W. Daniels, *J. Prakt. Chem.* [2] **110**, 235 (1925).
²⁸² E. Benary, H. Meyer, and K. Charisius, *Ber.* **59**, 108 (1926).
²⁸³ E. Benary and G. A. Bitter, *Ber.* **61**, 1057 (1928).
²⁸⁴ E. Benary, *Ber.* **61**, 2252 (1928).
²⁸⁵ J. Algar and J. McKenna, *Proc. Roy. Irish Acad.* **49**, 225 (1944); *Chem. Abstr.* **38**, 5503 (1944).
²⁸⁶ H. Rupe and F. Gisiger, *Helv. Chim. Acta* **8**, 338 (1925).
²⁸⁷ V. Ya. Grinshtein and A. P. Veverke, *Zh. Obshch. Khim.* **32**, 1077 (1962).
²⁸⁸ C. E. Grothaus and F. B. Dains, *J. Am. Chem. Soc.* **58**, 1334 (1936).
²⁸⁹ H. O. House, D. J. Reif, and R. L. Wasson, *J. Am. Chem. Soc.* **79**, 2490 (1957).
²⁹⁰ H. O. House, *J. Am. Chem. Soc.* **76**, 1235 (1954).
²⁹¹ L. Panizzi and M. Sbrillo Siena, *Gazz. Chim. Ital.* **73**, 335 (1943).
²⁹² R. O. Marielle and R. Standsfield, *J. Am. Chem. Soc.* **73**, 1368 (1951).
²⁹³ E. E. Royals and K. C. Brannock, *J. Am. Chem. Soc.* **75**, 2050 (1953).
²⁹⁴ I. L. Finar, *J. Chem. Soc.* **1961**, 674.
^{294a} T. V. Protopopova and A. P. Skoldinov, *Khim. Nauka i Promy.* **3**, 536 (1958).

shown recently that the mode of addition to 2-acetylcyclohexanone may be determined entirely by forming the enol-acetate of the acetyl group or by forming the enamine of the ring carbonyl group.²⁹⁵

Semicarbazide and hydroxymethylene ketones give isomeric carbamides depending on the conditions; the more labile carbamide may be converted into the more stable form by the action of heat or acid.^{159, 271, 296}



Acetals of β -keto aldehydes are hydrolyzed in acid media and hence under these conditions they give pyrazoles just as the ketoaldehydes themselves.²⁹⁷⁻³⁰⁰ Recently the bis-acetal of malondialdehyde has been used extensively for the synthesis of pyrazoles unsubstituted on the ring carbon atoms; the reaction yields single products since the bis-acetal is symmetrical.^{217, 271, 273, 301-307} Cyclization takes place in

²⁹⁵ B. Eistert and R. Wessendorf, *Ber.* **94**, 2590 (1961).

²⁹⁶ E. Cattelain and P. Chabrier, *Bull. Soc. Chim. France* **14**, 1101 (1947).

²⁹⁷ A. N. Nesmeyanov, N. K. Kochetkov, and M. N. Rybinskaya, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk* **1951**, 395.

²⁹⁸ K. Kaufmann and W. Stamm, *Fette, Seifen, Anstrichmittel* **59**, 946 (1957); *Chem. Abstr.* **54**, 1288 (1960).

²⁹⁹ W. Franke and R. Kraft, *Angew. Chem.* **67**, 395 (1955).

³⁰⁰ P. W. Brian, J. H. P. Petty, and P. T. Richmond, *Nature* **184**, 69 (1959).

³⁰¹ T. V. Protopopova and A. P. Skoldinov, *Zh. Obshch. Khim.* **27**, 1276 (1957).

³⁰² V. T. Klimko and A. P. Skoldinov, *Zh. Obshch. Khim.* **29**, 4027 (1959).

³⁰³ J. W. Copenhaver, U.S. Patent 2,515,160 (1950); *Chem. Abstr.* **44**, 8960 (1950).

³⁰⁴ P. Pino, *Gazz. Chim. Ital.* **80**, 768 (1950).

³⁰⁵ C. Antonio, *Corriere Farm.* **15**, 188 (1960); *Ref. Zh. Khim.* **1961**, 61252.

³⁰⁶ G. Losse, W. Hessler, and A. Barth, *Ber.* **91**, 150 (1958).

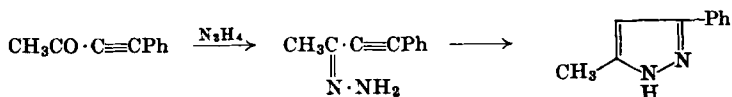
³⁰⁷ G. D. Byrkit and G. A. Michalek, *Ind. Eng. Chem.* **42**, 1862 (1950).

the presence of traces of strong acids necessary to hydrolyze the acetal groups. The reaction does not take place in alkaline or neutral media.^{217,308} A series of 1,3-dialdehyde derivatives of the form $R-C(CHO)=CHX$ (where $X = OH, OR', OAc, NR'_2$, halogen) give high yields of 4-substituted pyrazoles on reaction with hydrazines.³⁰⁹

Like β -keto esters, β -keto nitriles react smoothly with hydrazine; the latter give aminopyrazoles.^{78,310-321} Under the same conditions cyanoacetic ester and its derivatives give aminopyrazolones.³²²⁻³²⁵ The reaction of malononitrile is more complex, giving 1-substituted 3-cyanomethyl-4-cyano-5-aminopyrazole and products formed by further condensation.³²⁶

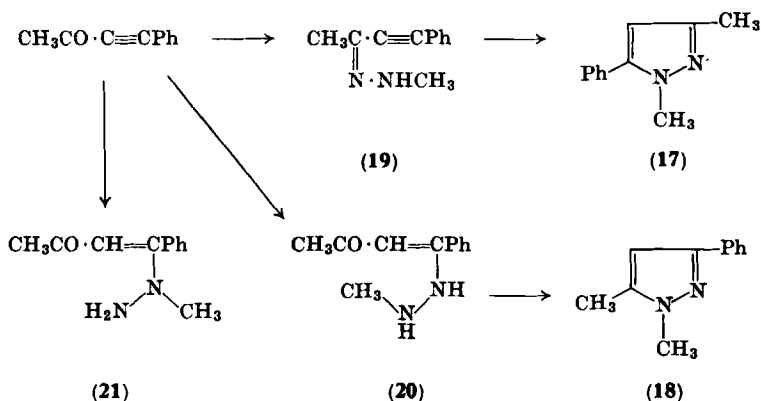
Recently, α,β -ethynyl ketones and aldehydes have become more accessible.³²⁷ The former give substituted hydrazones which cyclize to pyrazoles either spontaneously^{204, 273, 281, 328-333} or in the presence of acid.^{160, 328-331}

- ³⁰⁸ J. W. Copenhaver, U.S. Patent 2,527,533 (1950); *Chem. Abstr.* **45**, 1625 (1951).
³⁰⁹ V. T. Klimko, T. V. Protopopova, and A. P. Skoldinov, *Zh. Obshch. Khim.* **31**, 170 (1961).
³¹⁰ M. Lamant, *Bull. Soc. Chim. France* **1955**, 1396.
³¹¹ K. von Auwers, T. Bahr, and E. Frese, *Ann.* **441**, 68 (1925).
³¹² S. B. Coan and E. I. Becker, *J. Am. Chem. Soc.* **76**, 501 (1954).
³¹³ E. Mohr, *J. Prakt. Chem.* [2] **90**, 223 (1914).
³¹⁴ C. Bülow, *Ber.* **3401** (1910).
³¹⁵ R. Walther, *J. Prakt. Chem.* [2] **55**, 137 (1897).
³¹⁶ M. L. Bouveault, *Bull. Soc. Chim. France* [3] **4**, 647 (1890).
³¹⁷ M. Demetre-Vladesco, *Bull. Soc. Chim. France* [3] **6**, 815 (1891).
³¹⁸ C. Alberti, *Gazz. Chim. Ital.* **89**, 1017 (1959).
³¹⁹ F. Bell, *J. Chem. Soc.* **1941**, 285.
³²⁰ S. Coan and E. Becker, *J. Am. Chem. Soc.* **76**, 501 (1954).
³²¹ W. Logemann, L. Almirante, and L. Caprio, *Ber.* **87**, 1175 (1954).
³²² A. Weissberger and H. D. Porter, *J. Am. Chem. Soc.* **66**, 1849 (1944).
³²³ J. Druey and P. Schmidt, *Helv. Chim. Acta* **37**, 1828 (1954).
³²⁴ R. Metze and H. G. Kazmirowski, *Ber.* **91**, 1798 (1958).
³²⁵ R. K. Robins, *J. Am. Chem. Soc.* **78**, 784 (1956).
³²⁶ E. C. Taylor and K. S. Hartke, *J. Am. Chem. Soc.* **81**, 2452 (1959).
³²⁷ K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.* **1946**, 39.
³²⁸ M. P. L. Viguier, *Ann. Chim. Phys. (Paris)* [8] **28**, 433 (1913).
³²⁹ C. Moureu and R. Delange, *Bull. Soc. Chim. France* [3] **31**, 1337 (1904).
³³⁰ G. Dupont, *Bull. Soc. Chim. France* [4] **41**, 1167 (1927).
³³¹ A. Vaitiekunas, R. F. Miller, and F. F. Nard, *J. Org. Chem.* **16**, 1603 (1951).
³³² K. Bowden and E. R. H. Jones, *J. Chem. Soc.* **1946**, 953.
³³³ D. Nightingale and F. Wadsworth, *J. Am. Chem. Soc.* **67**, 416 (1945).



The reaction of acetylenic aldehydes^{160, 334} and their acetals^{160, 204, 274, 281, 328} with phenylhydrazines proceeds less readily.

Semicarbazide and 2,4-dinitrophenylhydrazine give only hydrazones,^{281, 327, 329, 335} although in certain earlier papers these were taken to be pyrazoles.^{160, 329} The rather more basic alkylhydrazines can form hydrazones or add directly to the acetylenic link. Thus 1-phenylbut-1-yn-3-one and methylhydrazine evidently form compounds **19** and **20**, as both isomeric pyrazoles were isolated after cyclization.⁸³ It is quite possible that compound **21** was also formed; this would form pyrazole **17** and not **18**.



In the majority of cases alkyl hydrazines give single pyrazoles.^{160, 328, 336, 337} In 1958 Bertrand established that allenic ketones give pyrazoles quantitatively with hydrazine.³³⁸ The reaction may be formulated as follows, the second stage being stabilization by aromatization. Acetylenic nitriles give aminopyrazoles with hydrazine.³³⁹

³³⁴ L. Claisen, *Ber.* **36**, 3664 (1903).

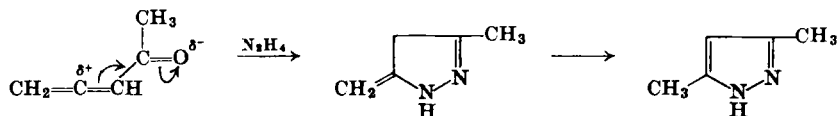
³³⁵ M. E. André, *Ann. Chim. Phys. (Paris)* [8] **29**, 540 (1913).

³³⁶ H. B. Henbest, *J. Chem. Soc.* **1952**, 4536.

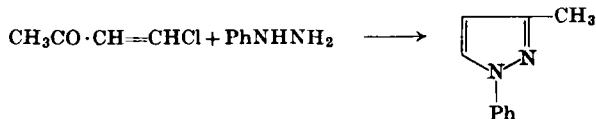
³³⁷ G. Østrup, "Referatenband XIV Internationaler Kongress für Reine und Angewandte Chemie," p. 24. Zürich, 1955.

³³⁸ M. Bertrand, *Compt. Rend.* **245**, 2306 (1957).

³³⁹ C. Moureu and I. Lazennec, *Bull. Soc. Chim. France* [4] **1**, 1071 (1907).



N. K. Kochetkov and A. N. Nesmeyanov showed that β -chlorovinyl ketones react with hydrazine in ethanolic solution to give high yields of 3-substituted pyrazoles.²⁹⁷ Unlike hydroxymethylene ketones, which by tautomerism give mixtures of isomeric pyrazoles, β -chlorovinyl ketones react with phenylhydrazine to give only one isomer, a point which was verified experimentally.³⁴⁰ This can only be explained



by assuming the initial formation of a hydrazone, followed by elimination of hydrogen chloride. As β -chlorovinyl ketones are accessible via the acetylenic synthesis³⁴¹ this path may be developed for the synthesis of 1,3-disubstituted pyrazoles.³⁴¹⁻³⁴⁵ A similar reaction takes place with β -rhodanyl-³⁴⁶ and β -(*p*-toluenesulfonyl)-vinyl ketones.³⁴⁷ It should be noted that sterically hindered compounds, such as 2-chloro-1-acetylcyclopent-1-ene, form only phenylhydrazones, which do not cyclize to pyrazoles.³⁴⁸ Similar pyrazole syntheses may be carried out using α,β -unsaturated aldehydes and ketones with substituents other than chlorine in the β -position. The following are examples:

³⁴⁰ J. Kosuge, H. Okeda, L. Teraishi, H. Ito, and S. Kosaka, *J. Pharm. Soc. Japan* **74**, 819 (1954); *Chem. Abstr.* **49**, 10273 (1955).

³⁴¹ N. K. Kochetkov, *Usp. Khim.* **24**, 32 (1955).

³⁴² T. Kosuge, H. Okeda, M. Aburatani, H. Ito, and S. Kosaka, *J. Pharm. Soc. Japan* **74**, 1086 (1954); *Chem. Abstr.* **49**, 11628 (1955).

³⁴³ N. K. Kochetkov, E. D. Khomutova, O. B. Mikhailova, and A. N. Nesmeyanov, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk* **1957**, 1181.

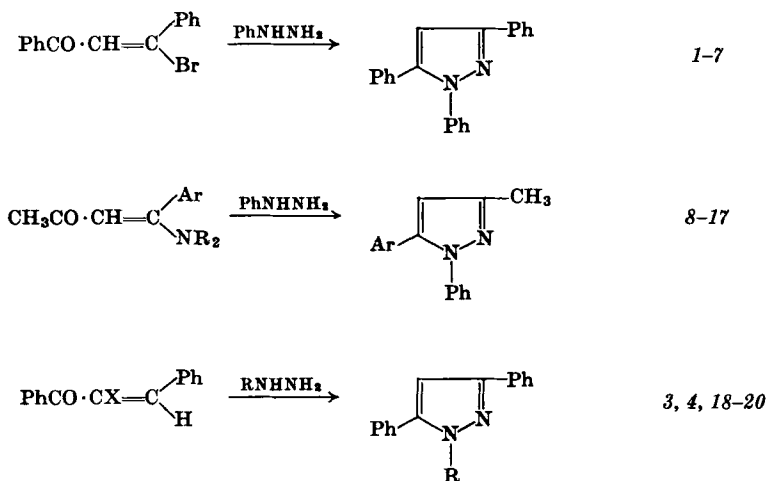
³⁴⁴ M. Julia, *Ann. Chim. (Paris)* [12] **5**, 595 (1950).

³⁴⁵ C. Alberti and G. Zerbi, *Farmaco (Pavia), Ed. Sci.* **16**, 527 (1961).

³⁴⁶ N. K. Kochetkov, *Dokl. Akad. Nauk SSSR* **82**, 593 (1952).

³⁴⁷ H. Kloosterziel and H. J. Backer, *Rec. Trav. Chim.* **71**, 361 (1952).

³⁴⁸ N. K. Kochetkov, E. E. Nifant'ev, and V. I. Shibaev, *Zh. Obshch. Khim.* **29**, 2324 (1959).

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^a (1) H. L. Davis, *J. Am. Chem. Soc.* **63**, 1677 (1941); (2) K. von Auwers and R. Hugel, *J. Prakt. Chem.* [2] **143**, 157 (1935); (3) M. P. L. Viguier, *Ann. Chim. Phys. (Paris)* [8] **28**, 433 (1913); (4) K. von Auwers and H. Broche, *Ber.* **55**, 3880; (5) R. D. Abell and W. Sidall, *J. Chem. Soc.* **1953**, 2804; (6) G. Wittig, *Ber.* **58**, 19 (1925); (7) C. L. Arcus and D. G. Smyth, *J. Chem. Soc.* **1955**, 34; (8) M. J. S. Dewar and F. E. King, *ibid.* **1945**, 114; (9) V. Ya. Grinshtein and A. P. Veverke, *Zh. Obshch. Khim.* **32**, 1077 (1962); (10) J. Pascual and F. Serratosa, *Ber.* **85**, 686 (1952); (11) A. Combes and C. Combes, *Bull. Soc. Chim. France* [3] **7**, 778 (1892); (12) E. Benary and M. Schmidt, *Ber.* **54**, 2157 (1921); (13) E. Benary and M. Hosenfeld, *ibid.* **55**, 3417 (1922); (14) E. Benary, H. Soenderop, and E. Bennowitz, *ibid.* **56**, 910 (1923); (15) E. Benary and W. Kereckhoff, *ibid.* **59**, 2548 (1926); (16) E. Benary, *ibid.* **60**, 1826 (1927); (17) G. Wittig and H. Blumenthal, *ibid.* **60**, 1085 (1927); (18) K. H. Bauer and M. Seyfarth, *ibid.* **63**, 2691 (1930); (19) K. von Auwers and W. Schmidt, *ibid.* **58**, 528 (1925); (20) G. V. Deshmukh and T. S. Wheeler, *J. Chem. Soc.* **1939**, 96.

In all these cases hydrazones are formed first and then, presumably, substituted pyrazolines which aromatize under the conditions of the reaction.³⁴⁹ Certainly acylhydrazines give hydrazones with such ketones,^{81, 276, 281, 328} and certain substituted pyrazolines, particularly halogenopyrazolines, are easily converted into pyrazoles (see accompanying tabulation). Pyrazoles may be synthesized from α,β -disubstituted carbonyl compounds and the corresponding halides, from which the substituents may be cleaved.

³⁴⁹ A. N. Kost and V. V. Ershov, *Usp. Khim.* **27**, 431 (1958).

| Compound | Reference ^a |
|--|------------------------|
| $\begin{array}{c} \text{Ph} \cdot \text{CO} \cdot \text{CH} \cdot \text{CH}_2 \cdot \text{Br} \\ \\ \text{N}(\text{CH}_3)_2 \end{array}$ | 1 |
| $\begin{array}{c} \text{Ar} \cdot \text{CO} \cdot \text{CH} \text{---} \text{CH} \cdot \text{CH}_3 \\ \diagdown \quad \diagup \\ \text{N} \\ \\ \text{R} \end{array}$ | 2-6 |
| $\begin{array}{l} \text{CHBr}_2 \cdot \text{CH}_2 \cdot \text{CH}(\text{OCOCH}_3)\text{Br} \\ \text{CHBr}_2 \cdot \text{CH}_2 \cdot \text{CH}(\text{OR})_2 \\ \text{CHBr}_2 \cdot \text{CH}_2 \cdot \text{CH}(\text{OR})\text{Cl} \\ \text{CHCl}_2 \cdot \text{CH}_2 \cdot \text{CHO} \\ \text{BrCH}(\text{OR}) \cdot \text{CH}_2 \cdot \text{CHO} \end{array} \quad \left. \vphantom{\begin{array}{l} \text{CHBr}_2 \cdot \text{CH}_2 \cdot \text{CH}(\text{OCOCH}_3)\text{Br} \\ \text{CHBr}_2 \cdot \text{CH}_2 \cdot \text{CH}(\text{OR})_2 \\ \text{CHBr}_2 \cdot \text{CH}_2 \cdot \text{CH}(\text{OR})\text{Cl} \\ \text{CHCl}_2 \cdot \text{CH}_2 \cdot \text{CHO} \\ \text{BrCH}(\text{OR}) \cdot \text{CH}_2 \cdot \text{CHO} \end{array}} \right\}$ | 7, 8 |
| $\begin{array}{c} \text{Ar} \cdot \text{CO} \cdot \text{CH} \text{---} \text{CH} \cdot \text{R} \\ \diagdown \quad \diagup \\ \text{O} \end{array}$ | 9-13 |
| $\begin{array}{l} \text{HCO} \cdot \text{CH}_2 \cdot \text{CHBr}_2 \\ \text{ClCH}=\text{CH} \cdot \text{CHO} \\ \text{R} \cdot \text{CO} \cdot \text{CH}_2 \cdot \text{CHCl}_2 \end{array}$ | 8, 14 15-16 17 |

^a (1) A. N. Kost and V. V. Ershov, *Usp. Khim.* **27**, 431 (1958); (2) N. H. Cromwell and G. Mercer, *J. Am. Chem. Soc.* **79**, 3819 (1957); (3) N. H. Cromwell and R. Mohrbacher, *ibid.* **75**, 6252 (1953); (4) N. H. Cromwell and H. Hoeksma, *ibid.* **71**, 716 (1949); (5) N. H. Cromwell, N. Barker, R. Wankel, P. Vanderhorst, E. Olson, and J. Hill, *ibid.* **73**, 1044 (1951); (6) N. H. Cromwell and M. A. Craff, *J. Org. Chem.* **17**, 414 (1952); (7) T. V. Protopopova and A. P. Skoldinov, *Khim. Nauka i Promy.* **3**, 536 (1958); (8) *idem.*, *Zh. Obshch. Khim.* **26**, 3355 (1956); (9) H. O. House, *J. Am. Chem. Soc.* **78**, 2298 (1956); (10) H. Jörlander, *Ber.* **49**, 2782 (1916); (11) N. H. Cromwell and R. Setterquist, *J. Am. Chem. Soc.* **76**, 5752 (1954); (12) O. Widman, *Ann.* **400**, 86 (1913); (13) S. Bodforss, *Ber.* **49**, 2795 (1916); (14) P. Pino and R. Ercoli, *Gazz. Chim. Ital.* **81**, 757 (1951); (15) T. V. Protopopova and A. P. Skoldinov, *Zh. Obshch. Khim.* **29**, 963 (1959); (16) A. Gaudiano, A. Quilico, and A. Ricca, *Atti Accad. Nazl. Lincei* **21**, 253 (1956); (17) V. T. Klimko, V. A. Mikhalev, and A. P. Skoldinov, *Zh. Obshch. Khim.* **27**, 370 (1957).

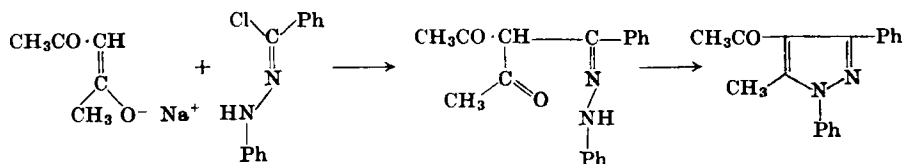
A reaction which is peculiar to epichlorhydrin was shown by Finar³⁵⁰ to give a pyrazole from a phenylhydrazine. The β -substituted phenylhydrazine (**21**), formed at first, is oxidized by a second molecule of the phenylhydrazine to a hydrazone, possibly via an azo-compound; the unstable 4-hydroxypyrazoline (**22**) formed by cyclization readily splits off water to give 1-phenylpyrazole.

The cleavage of the elements of water takes place by the usual *trans*-elimination; hydroxy- and aminopyrazolines without a hydrogen atom *trans* to the substituent are fairly stable.³⁵¹ For the interaction of acetylene oxides with hydrazines see Perveev and Ershova.³⁵²

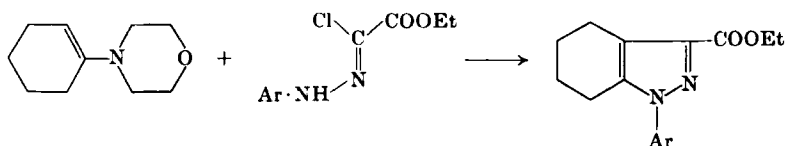
³⁵⁰ I. L. Finar and K. E. Godfrei, *J. Chem. Soc.* **1954**, 2293.

³⁵¹ H. Jörlander, *Ber.* **49**, 2782 (1916).

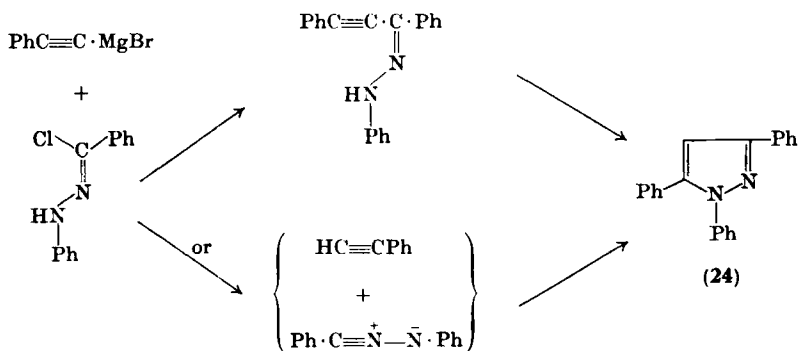
³⁵² F. Ya. Perveev and V. I. Ershova, *Zh. Obshch. Khim.* **30**, 3554 (1960).



takes place with β -keto esters.^{355, 361, 362} The use of enamines widens the scope of this reaction to include various monoketones.³⁶³ As a variant of this method, enamines are treated with isothiocyanates and then with hydrazine,³⁶⁴ to give 3-aminopyrazoles. Grünanger³⁶⁵ has



recently described the reaction of α -chlorobenzaldehyde phenylhydrazone with phenylethynyl magnesium bromide, which gives 1,3,5-triphenylpyrazole (24), perhaps via the phenylhydrazone of an ethynyl ketone, or maybe via a diphenyl nitrile imine:



³⁶¹ R. Justoni, *Gazz. Chim. Ital.* **68**, 49 (1938).

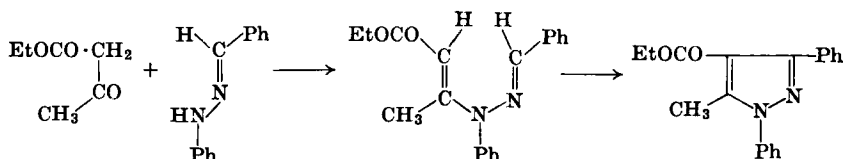
³⁶² R. Justoni and R. Fusco, *Gazz. Chim. Ital.* **68**, 59 (1938).

³⁶³ R. Fusco, G. Bianchetti, and D. Pocar, *Gazz. Chim. Ital.* **91**, 1233 (1961).

³⁶⁴ S. Hünig and K. Hübner, *Ber.* **95**, 937 (1962).

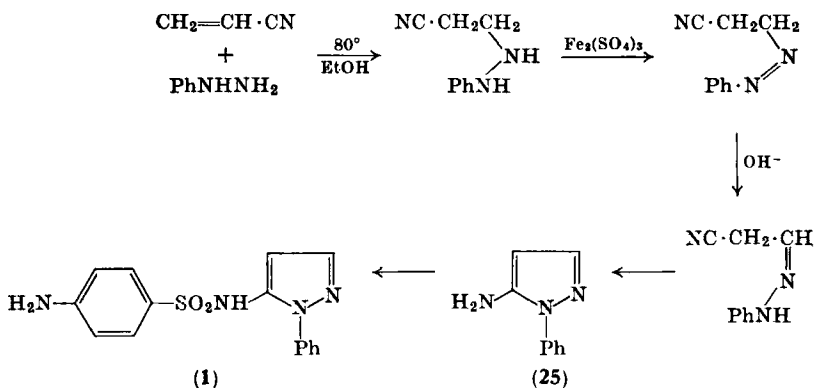
³⁶⁵ P. Grünanger and M. R. Langella, *Gazz. Chim. Ital.* **90**, 229 (1960).

Minnuni^{366, 367} observed that, in the presence of anhydrous zinc chloride, phenylhydrazones of aromatic aldehydes react with acetoacetic ester and its analogs to form derivatives of β -aminocrotonic ester, which on cyclization and dehydrogenation give the corresponding pyrazoles.



Propiolic esters react with phenylhydrazines similarly.^{368, 369}

Schmidt and Druey³⁷⁰ synthesized 1-phenyl-5-aminopyrazole (25) by a novel method as follows:



The aminopyrazole made available by this method was converted to the sulfonamide (1) sold under the name Orisul and patented in Switzerland as one of the best long-acting sulfonamides.³⁷¹

³⁶⁶ G. Minunni, *Gazz. Chim. Ital.* **55**, 202 (1925).

³⁶⁷ G. Minunni and S. d'Urso, *Gazz. Chim. Ital.* **58**, 691 (1928).

³⁶⁸ H. G. Garg, *J. Org. Chem.* **26**, 948 (1961).

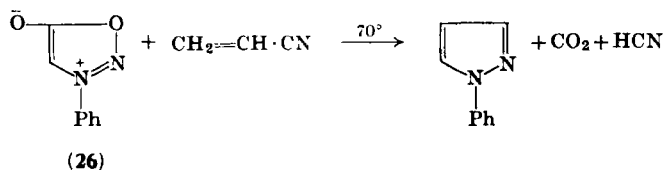
³⁶⁹ C. Musante, *Gazz. Chim. Ital.* **67**, 682 (1931).

³⁷⁰ P. Schmidt and J. Druey, *Helv. Chim. Acta* **41**, 307 (1958).

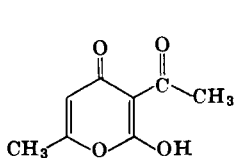
³⁷¹ J. Jucker, *Angew. Chem.* **71**, 321 (1959).

B. THE CONVERSION OF HETEROCYCLIC COMPOUNDS INTO PYRAZOLES

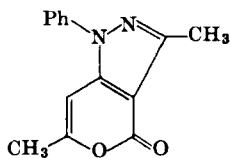
The reactions between sydnones (e.g. **26**) and unsaturated compounds frequently yield pyrazoles. Pyrazolines are produced by 1,3-dipolar addition to alkenes, and pyrazoles from alkynes.³⁷²⁻³⁷⁴ The cyanopyrazolines formed from α,β -unsaturated nitriles are immediately converted to pyrazoles.³⁷³



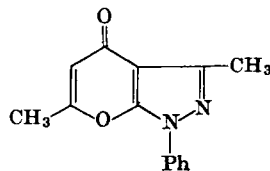
In 1905 Stollé³⁷⁵ observed that dehydroacetic acid (**27**) reacted with phenylhydrazine to give a pyrazolocoumarin, later shown³⁷⁶ to have the structure **28** rather than **29**, which was assigned at first.



(27)



(28)



(29)

Kizhner^{377, 378} showed that 2,6-dimethyl- γ -pyrone and hydrazine react in a different way, the pyrone ring opening and a more stable

³⁷² V. G. Yashunskii, V. R. Vasil'eva, and M. N. Shchukina, *Zh. Obshch. Khim.* **30**, 698 (1960).

³⁷³ V. R. Vasil'eva, V. G. Yashunskii, and M. N. Shchukina, *Zh. Obshch. Khim.* **31**, 1501 (1961).

³⁷⁴ R. Huisgen, R. Grashey, H. Gotthardt, and R. Schmidt, *Angew. Chem.* **74**, 29 (1962).

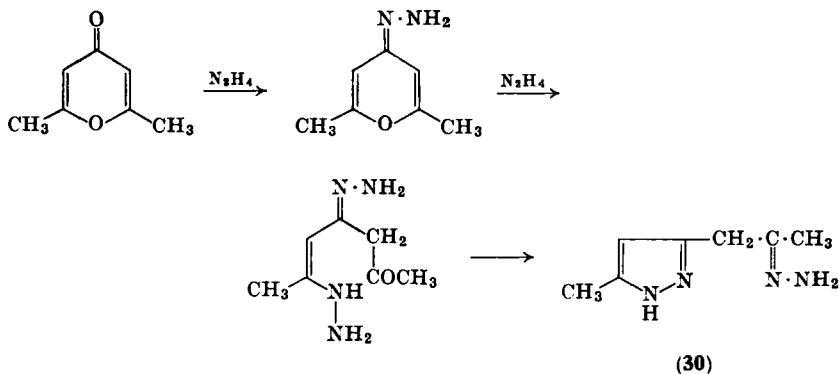
³⁷⁵ R. Stollé, *Ber.* **38**, 3023 (1905).

³⁷⁶ E. Benary, *Ber.* **43**, 1070 (1910).

³⁷⁷ N. M. Kizhner, *Zh. Russ. Fiz.-Khim. Obshch.* **55**, 539 (1923).

³⁷⁸ N. M. Kizhner, "Studies in the Field of Organic Chemistry," p. 482. Akad. Nauk SSSR, Moscow, Leningrad, 1937 (in Russian).

pyrazole ring (30) being formed by recyclization. Subsequently it was established^{33, 323, 379-381} that γ -pyrone itself and many substituted γ -pyrones react similarly with hydrazine and arylhydrazines. In the papers of some Indian authors^{382, 383} the compounds formed are



incorrectly formulated as hydrazones of *N*-amino- γ -pyridone (31). Alberti³⁸⁴⁻³⁹⁵ studied this reaction systematically and showed that the conversion of such heterocyclic structures into pyrazoles is observed in almost all cases where the starting material is derived from a 1,3-dicarbonyl compound, its enol, or a derivative of the enol of an

³⁷⁹ R. G. Jones, U.S. Patent 2,785,177 (1957); *Chem. Abstr.* **51**, 13933 (1957).

³⁸⁰ C. Ainsworth and R. G. Jones, *J. Am. Chem. Soc.* **76**, 3172 (1954).

³⁸¹ W. Borsche and B. K. Blount, *Ber.* **65B**, 820 (1932).

³⁸² S. S. Deshapande, Y. V. Dingankar, and D. N. Kopil, *J. Indian Chem. Soc.* **11**, 595 (1934).

³⁸³ D. N. Bedekar, R. P. Kaushal, and S. S. Deshapande, *J. Indian Chem. Soc.* **12**, 465 (1935).

³⁸⁴ C. Alberti, *Gazz. Chim. Ital.* **85**, 245 (1955).

³⁸⁵ C. Alberti, *Gazz. Chim. Ital.* **87**, 720 (1957).

³⁸⁶ C. Alberti, *Gazz. Chim. Ital.* **87**, 736 (1957).

³⁸⁷ C. Alberti, *Gazz. Chim. Ital.* **87**, 751 (1957).

³⁸⁸ C. Alberti, *Gazz. Chim. Ital.* **87**, 762 (1957).

³⁸⁹ C. Alberti, *Gazz. Chim. Ital.* **87**, 781 (1957).

³⁹⁰ C. Alberti, *Gazz. Chim. Ital.* **87**, 772 (1957).

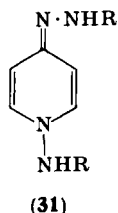
³⁹¹ C. Alberti, "Atti XLV Riunione Soc. Italiana Progresso Sci.," Napoli, 1954, p. 20. Rome, 1956.

³⁹² C. Alberti, *Gazz. Chim. Ital.* **69**, 568 (1939).

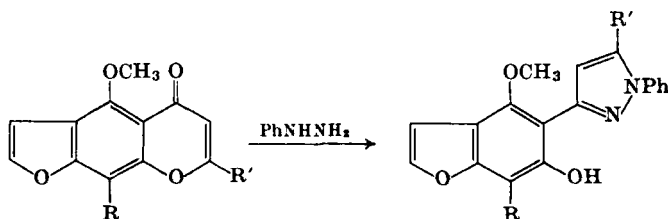
³⁹³ C. Alberti, *Gazz. Chim. Ital.* **67**, 238 (1937).

³⁹⁴ C. Alberti, *Gazz. Chim. Ital.* **77**, 398 (1947).

³⁹⁵ C. Alberti, *Gazz. Chim. Ital.* **87**, 729 (1957).



aldehyde or ketone substituted on the double bond. Chromones, flavones, flavanones, and their sulfur analogs react like pyrones with hydrazine on refluxing for 1–2 hours in ethanol solution.^{389, 396–399} The reaction was used to establish the structures of natural products in the kellin series.^{400–406}



The ester of isodehydroacetic acid, a derivative of α -pyrone, forms a 3-methylpyrazolin-5-one with hydrazine,⁴⁰⁷ although in certain papers α -pyrones and hydrazines are said to form 4-acylearboxylic acid hydrazides⁴⁰⁸ and *N*-aminopyridones.⁴⁰⁹ A point of interest is that even nitrogenous heterocyclic compounds such as quinolin-4-ones

³⁹⁶ W. Baker, J. B. Harborne, and W. D. Ollis, *J. Chem. Soc.* **1952**, 1303.

³⁹⁷ J. Schmutz and R. Hirt, *Helv. Chim. Acta* **36**, 132 (1953).

³⁹⁸ W. Baker, G. C. Clarke, and J. B. Harborne, *J. Chem. Soc.* **1954**, 998.

³⁹⁹ P. Venturella, A. Bellino, and S. Cusmano, *Ann. Chim. (Rome)* **51**, 34 (1961).

⁴⁰⁰ C. Musante and S. Fatutta, *Ann. Chim. (Rome)* **45**, 918 (1955).

⁴⁰¹ W. Baker and V. Butt, *J. Chem. Soc.* **1949**, 2142.

⁴⁰² A. F. Thomas and A. Marxer, *Helv. Chim. Acta* **91**, 1898 (1958).

⁴⁰³ A. Mustafa, M. Kamel, M. A. Allam, A. H. El-Sayed Harhash, and A. E. A. A. Hassan, *J. Am. Chem. Soc.* **78**, 5011 (1956).

⁴⁰⁴ M. Ridi, P. Papini, S. Checchi, and F. Conti, *Gazz. Chim. Ital.* **84**, 781 (1954).

⁴⁰⁵ A. Schönberg and M. M. Sidky, *J. Am. Chem. Soc.* **75**, 5128 (1953).

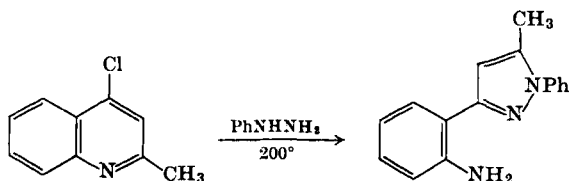
⁴⁰⁶ C. Musante and S. Fatutta, *Farmaco (Pavia), Ed. Sci.* **9**, 328 (1954).

⁴⁰⁷ R. H. Wiley, A. J. Hart, R. P. Davis, and N. R. Smith, *J. Am. Chem. Soc.* **76**, 4931 (1954).

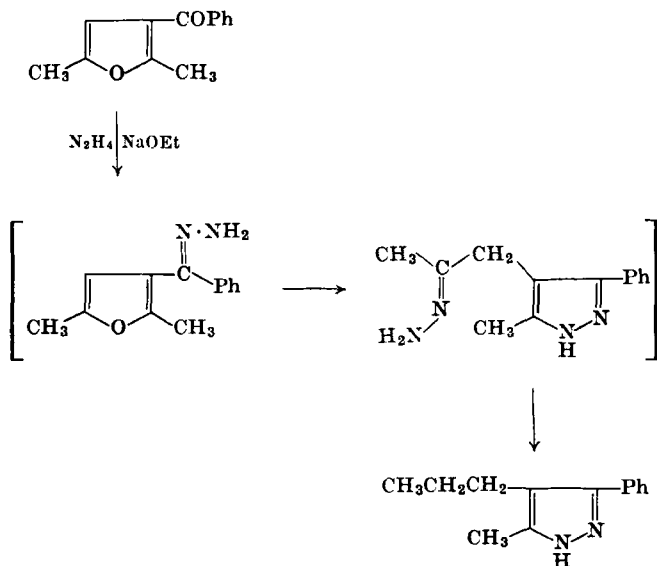
⁴⁰⁸ G. Chavanne, *Compt. Rend.* **133**, 167 (1901).

⁴⁰⁹ U. Chiodoni, *Chim. Ind. (Milan)* **45**, 968 (1963).

and 4-chloro- and 4-bromo-quinolines^{390, 410-412} undergo rupture of the heterocyclic ring with subsequent conversion to pyrazoles. The conditions of the reaction, however, are somewhat more severe.



The presence of a carbonyl substituent in the β -position of the hetero-cycle is essential for the cleavage of five-membered rings. The compounds of this type which have been investigated most thoroughly are 3-acetylindoles.^{287, 384-388} At 160–170° 3-acetylindole and hydrazine hydrate give 3-(*o*-aminophenyl)-5-methylpyrazole, the structure of which was proved by deamination. Other 3-acetylindoles, their hydrazones, and azines, react analogously.³⁸⁵ For the mechanism of the reaction see Alberti.^{384, 391} The reaction requires a fourfold excess of hydrazine hydrate,³⁸⁷ preferably a polar solvent,³⁸⁸ and about



⁴¹⁰ E. Koenigs and J. Freund, *Ber.* **80**, 143 (1947).

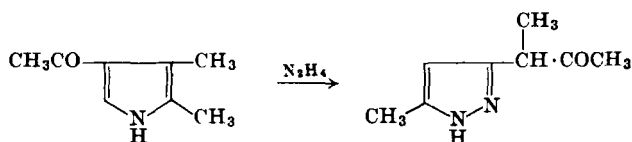
⁴¹¹ C. Musante and V. Parrini, *Gazz. Chim. Ital.* **84**, 209 (1954).

⁴¹² I. L. Finar and A. B. Simmonds, *J. Chem. Soc.* **1958**, 200.

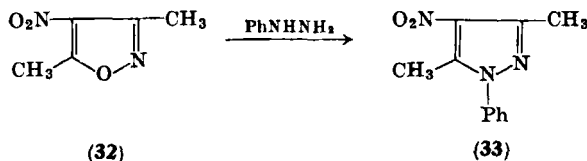
0.1 mole of hydrazine hydrochloride,³⁸⁶ which is characteristic for the addition of amines to activated double bonds.

Under these conditions 3-benzoyl-2,5-dimethylfuran undergoes both conversion to a pyrazole and Wolff-Kishner reduction of the side-chain.⁴¹³

The thiophene ring of 3-benzoylthiocoumarone opens and gives *o*-mercaptophenylpyrazole together with the corresponding disulfide.³⁸⁴ Similarly, 3-acylpyrroles are converted to pyrazoles.^{359, 414}



However, it is known that some acylpyrroles on heating with hydrazine in alkaline solution lose the acyl group,^{415, 416} and, further, in a series of papers^{416, 417} the successful application of the Wolff-Kishner reaction without affecting the ring and substituents is described. Thus, further study of the reaction of acylpyrroles is called for. The conversion of certain ketopyridazines to the corresponding pyrazole carboxylic acids has been recorded.⁴¹⁸⁻⁴²¹ To this group of reactions should be added that of isoxazoles with hydrazine. Thus on boiling phenylhydrazine with 3,5-dimethyl-4-nitroisoxazole (32), 1-phenyl-3,5-dimethyl-4-nitropyrazole (33) is formed.⁴²²



⁴¹³ P. S. Bailey, S. S. Bath, W. F. Thomsen, H. H. Nelson, and E. E. Kawas, *J. Org. Chem.* **21**, 297 (1956).

⁴¹⁴ C. Alberti, *Farmaco (Pavia), Ed. Sci.* **12**, 3 (1957).

⁴¹⁵ L. Knorr and R. Hess, *Ber.* **45**, 2631 (1912).

⁴¹⁶ H. Fischer and H. Ammann, *Ber.* **56**, 2319 (1923).

⁴¹⁷ H. Fischer and B. Bützer, *Ber.* **61**, 1068 (1928).

⁴¹⁸ V. Grinšteins and G. Čipens, *Latvijas PSR Zinatnu Akad. Vestis, Kim. Ser.* **1**, 65 (1962).

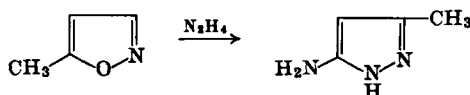
⁴¹⁹ L. Claisen, *Ann.* **278**, 261 (1894).

⁴²⁰ L. Claisen, *Ann.* **295**, 301 (1897).

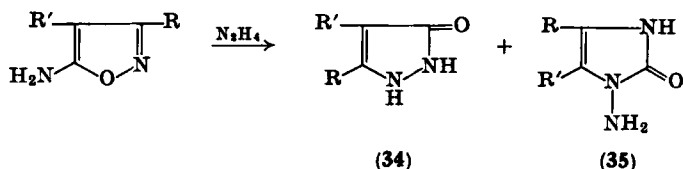
⁴²¹ F. Ach, *Ann.* **253**, 46 (1889).

⁴²² C. Musante, *Gazz. Chim. Ital.* **72**, 537 (1942).

4- or 5-Alkylisoxazoles and hydrazine or substituted hydrazines give 5-aminopyrazoles, though only in small yield.⁴²³⁻⁴²⁷ Similarly,



5-aminoisoxazoles are converted into the corresponding pyrazolinones (34) or *N*-aminoimidazolinones (35).^{428, 429} The susceptibility of the



isoxazole ring to attack by nucleophiles, in this case hydrazine, is responsible for these reactions.⁴³⁰⁻⁴³⁶ Concerning the conversion of heterocyclic compounds to pyrazoles, see also Beyer, Sandstrom, and others.⁴³⁷⁻⁴⁴³ Reactions of furans with hydrazine are described

⁴²³ F. R. Japp and F. Klingemann, *Ann.* **247**, 190 (1888).

⁴²⁴ V. Meyer, *Ber.* **21**, 11 (1888).

⁴²⁵ C. Musante, *Gazz. Chim. Ital.* **75**, 109 (1945).

⁴²⁶ F. Bell, *J. Chem. Soc.* **1941**, 285.

⁴²⁷ L. Claisen, *Ber.* **42**, 59 (1909).

⁴²⁸ H. Kano, *J. Pharm. Soc. Japan* **73**, 383 (1953).

⁴²⁹ H. Kano, *J. Pharm. Soc. Japan* **73**, 387 (1953).

⁴³⁰ R. A. Barnes, in "Heterocyclic Compounds" (R. C. Elderfield, ed.), Vol. 5, p. 452. Wiley, New York, 1957.

⁴³¹ S. Cusmano, *Gazz. Chim. Ital.* **70**, 227 (1940).

⁴³² S. Cusmano, *Gazz. Chim. Ital.* **69**, 594 (1939).

⁴³³ G. S. D'Alcontres, *Gazz. Chim. Ital.* **80**, 44 (1950).

⁴³⁴ S. Cusmano and T. Tiberio, *Gazz. Chim. Ital.* **78**, 896 (1948).

⁴³⁵ T. S. Gardner, F. A. Smith, and E. Wenis, and J. Lee, *J. Org. Chem.* **21**, 530 (1956).

⁴³⁶ C. Musante and A. Stener, *Gazz. Chim. Ital.* **89**, 1579 (1960).

⁴³⁷ H. Beyer, E. Bulka, G. Wolter, F. W. Beckhaus, and H. Lemke, *Wiss. Z. E.M. Arndt Univ. Greifswald, Math. Naturwiss. Reihe* **6**, 303 (1956-1957).

⁴³⁸ J. Sandstrom, *Arkiv Kemi*, **15**, 195 (1960).

⁴³⁹ C. Goldschmidt, *Ber.* **28**, 2952 (1895).

⁴⁴⁰ C. Musante, *Gazz. Chim. Ital.* **75**, 109 (1945).

⁴⁴¹ I. L. Finar, *J. Chem. Soc.* **1958**, 4094.

⁴⁴² N. S. Vul'fson and R. B. Zhurin, *Zh. Obshch. Khim.* **31**, 3381 (1961).

⁴⁴³ N. S. Vul'fson and R. B. Zhurin, *Zh. Obshch. Khim.* **32**, 991 (1962).

(conversion to pyrazoles,^{229, 444} to pyridines,⁴⁴⁵ and to pyridazines^{444, 446}), and for reactions of various other heterocyclic compounds with substituted hydrazines see Gever, Drew *et al.*, Chattaway, and others.⁴⁴⁷⁻⁴⁵¹

C. SYNTHESIS OF PYRAZOLES FROM ALIPHATIC DIAZO COMPOUNDS

Aliphatic diazo compounds and olefins react to form pyrazolines^{452, 453}; similarly, diazomethane and propargyl alcohol (prop-2-yn-1-ol) give 3-hydroxymethylpyrazole.^{454, 455} Usually in this type of reaction the triple bond of the acetylene is activated by an aldehyde group,⁴⁵⁶⁻⁴⁵⁹ a ketone group,³³² a carboxyl group,^{460, 461} or an alkoxycarbonyl group.^{389, 462} (See also reference 462*a*.) Von Auwers' rule is usually observed in these additions,^{458, 462-464} but certain exceptions are known. Thus, diazomethane and propargyl alcohol give 3% of 4-hydroxymethylpyrazole besides the 3-hydroxymethyl compound,⁴⁵⁴ and the methyl ester of phenylacetylene carboxylic acid reacts with methyl diazoacetate to form both possible isomers (36 and 37) in approximately equal quantities.⁴⁶²

⁴⁴⁴ N. Clauson-Kaas and F. Limberg, *Acta Chem. Scand.* **1**, 619 (1947).

⁴⁴⁵ K. Aso, *Bull. Inst. Phys. Chem. Res. (Tokyo)* **18**, 180 (1939); *Chem. Abstr.* **34**, 3273 (1940).

⁴⁴⁶ R. Seka and H. Preisseecker, *Monatsh.* **57**, 71 (1931).

⁴⁴⁷ G. Gever, *J. Am. Chem. Soc.* **76**, 1283 (1954).

⁴⁴⁸ H. D. K. Drew, H. H. Hatt, and F. A. Hobart, *J. Chem. Soc.* **1937**, 33.

⁴⁴⁹ F. D. Chattaway and D. R. Ainsworth, *J. Chem. Soc.* **1933**, 1624.

⁴⁵⁰ P. J. Russel, *J. Am. Chem. Soc.* **75**, 5375 (1953).

⁴⁵¹ G. Crippa and M. Guarneri, *Farmaco (Pavia), Ed. Sci.* **10**, 691 (1955).

⁴⁵² R. Huisgen, *Angew. Chem.* **67**, 439 (1955); R. Locquin and R. Heilmann, *Compt. Rend.* **181**, 120 (1925).

⁴⁵³ I. A. D'yakonov, "Aliphatic Diazocompounds." Goskhimisdats, Leningrad, 1958 (in Russian).

⁴⁵⁴ R. G. Jones, *J. Am. Chem. Soc.* **71**, 3994 (1949).

⁴⁵⁵ E. Mugnaini and P. Grünanger, *Atti Accad. Nazl. Lincei* **14**, 95 (1953).

⁴⁵⁶ R. Hüttel and A. Gebhardt, *Ann.* **558**, 34 (1947).

⁴⁵⁷ R. Hüttel, *Ann.* **585**, 115 (1954).

⁴⁵⁸ R. Hüttel, *Ber.* **74B**, 1680 (1941).

⁴⁵⁹ K. Henkel and F. Weygand, *Ber.* **76**, 812 (1943).

⁴⁶⁰ E. Buchner, *Ber.* **22**, 842 (1889).

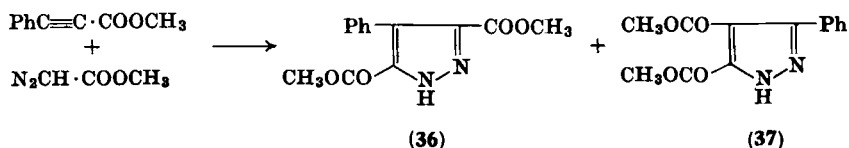
⁴⁶¹ H. von Pechmann, *Ber.* **31**, 2950 (1898).

⁴⁶² K. von Auwers and O. Ungemach, *Ber.* **66**, 1205 (1933).

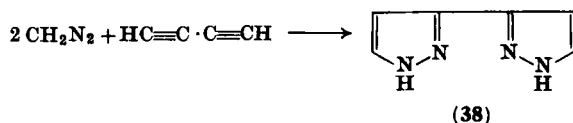
^{462a} B. C. Saunders and P. Simpson, *J. Chem. Soc.* **1963**, 3351.

⁴⁶³ K. von Auwers and O. Ungemach, *Ber.* **66**, 1690 (1933).

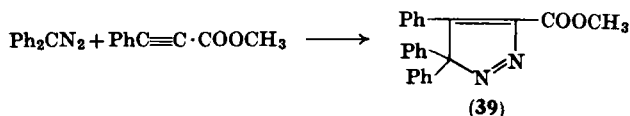
⁴⁶⁴ K. von Auwers and E. Cauer, *Ann.* **470**, 284 (1928).



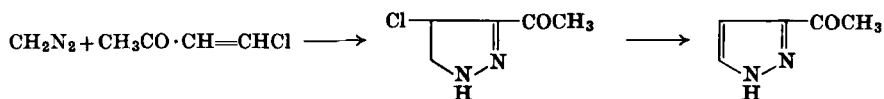
Acetylene itself and alkyl- and aryl-acetylenes react with diazomethane under more severe conditions, such as 2–5 atmospheres, 20–40°. ^{465–469} By this method 3,3'-dipyrazolyl (38) was synthesized



from diacetylene. Under similar conditions, disubstituted diazo compounds form pyrazolenines (4*H*-pyrazoles) (39). ^{456, 467, 470–472}



The place of an acetylene in these reactions may be taken by an olefin substituted by a group capable of elimination during the reaction. Thus, aliphatic diazo compounds and vinyl halides give pyrazoles, ⁴⁷³ whereas diazomethane and β -chlorovinyl ketones give



⁴⁶⁵ R. Kuhn and K. Henkel, *Ann.* **549**, 279 (1941).

⁴⁶⁶ W. Kirmse and L. Horner, *Ann.* **614**, 1 (1958).

⁴⁶⁷ J. Van Alpen, *Rec. Trav. Chim.* **62**, 485 (1943).

⁴⁶⁸ H. Reimlinger, *Ber.* **92**, 970 (1959).

⁴⁶⁹ C. Alberti and C. Tironi, *Farmaco (Pavia), Ed. Sci.* **17**, 468 (1962).

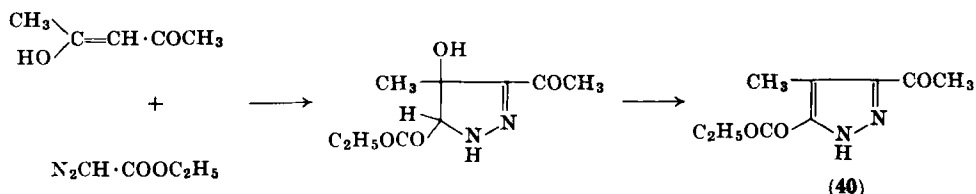
⁴⁷⁰ O. Diels and H. König, *Ber.* **71**, 1179 (1938).

⁴⁷¹ R. Hüttel, J. Riedel, H. Martin, and K. Franke, *Ber.* **93**, 1425 (1960).

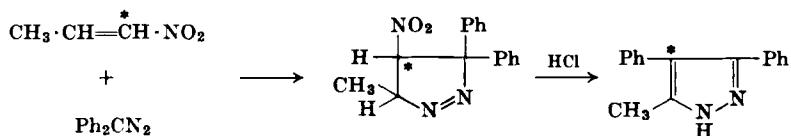
⁴⁷² K. Heyns and A. Heine, *Angew. Chem.* **73**, No. 2, 64 (1961).

⁴⁷³ E. Oliveri-Mandalà, *Gazz. Chim. Ital.* **40**, Part I, 117 (1910).

3-acylpyrazoles,⁴⁷³⁻⁴⁷⁸ via the unstable 4-chloropyrazolines. Similarly, ethyl diazoacetate reacts with the enol form of acetylacetone to yield a pyrazole (40).^{193, 479-483}



Cases are known where pyrazoles are formed from aliphatic diazo compounds and cyano-olefins,^{462, 463} or nitro-olefins, the latter reaction being studied systematically by Parham and co-workers, who established that the relatively stable nitropyrzolines initially formed eliminate nitrous acid when heated with acid.⁴⁸⁴⁻⁴⁸⁶ (See also reference 486a.) When the diazo compound is *gem*-disubstituted, a pyrazole is formed by migration of one of the groups, which was



⁴⁷⁴ A. N. Nesmeyanov and N. K. Kochetkov, *Dokl. Akad. Nauk SSSR* **77**, 65 (1951).

⁴⁷⁵ A. N. Nesmeyanov and N. K. Kochetkov, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk* **1951**, 686.

⁴⁷⁶ G. P. Rice, *J. Am. Chem. Soc.* **52**, 2094 (1930).

⁴⁷⁷ L. N. Owen and H. M. Babatunde Somade, *J. Chem. Soc.* **1947**, 1030.

⁴⁷⁸ N. K. Kochetkov, I. Ambrush, and A. I. Usov, *Zh. Obshch. Khim.* **29**, 2578 (1959).

⁴⁷⁹ A. Klages, *J. Prakt. Chem.* [2] **65**, 387 (1902).

⁴⁸⁰ G. F. Bettinetti, G. Desimoni, and P. Grünanger, *Gazz. Chim. Ital.* **93**, 150 (1963).

⁴⁸¹ C. D. Hurd and S. C. Lui, *J. Am. Chem. Soc.* **57**, 2656 (1935).

⁴⁸² D. W. Adamson and J. Kenner, *J. Chem. Soc.* **1935**, 286.

⁴⁸³ I. L. Finar and B. H. Walter, *J. Chem. Soc.* **1960**, 1588.

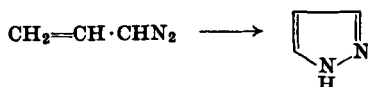
⁴⁸⁴ W. E. Parham and J. L. Bleasdale, *J. Am. Chem. Soc.* **73**, 4664 (1951).

⁴⁸⁵ W. E. Parham and J. L. Bleasdale, *J. Am. Chem. Soc.* **72**, 3843 (1950).

⁴⁸⁶ W. E. Parham and W. R. Hasek, *J. Am. Chem. Soc.* **76**, 799 (1954).

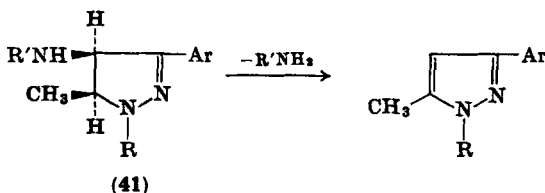
^{486a} R. Fusco and S. Rossi, *Rend. Ist. lombardo sci. Pt I* **93**, 143, 334 (1959).

proved by experiments using C^{14} .⁴⁸⁷ It is interesting to note that α,β -unsaturated diazo compounds may isomerize to pyrazoles⁴⁸⁰⁻⁴⁸²; vinyl diazomethane, for example, isomerizes in 36 hours at room temperature to pyrazole itself.²⁹⁶



D. SYNTHESIS OF PYRAZOLES FROM PYRAZOLES

Pyrazolines may be obtained readily from α,β -unsaturated aldehydes or ketones and aliphatic diazo compounds.^{44,349} Convenient syntheses have been worked out using Mannich bases,⁴⁸⁸⁻⁴⁹⁴ by the cyclization of aldehydo- and keto-azines.⁴⁹⁵⁻⁴⁹⁹ The conversion of a number of 4- and 5-substituted pyrazolines to the corresponding pyrazoles by *trans*-elimination was noted above. The 4-amino-pyrazolines with the appropriate configuration (41) readily eliminate



⁴⁸⁷ W. E. Parham, H. Braxton, and P. O'Connor, *J. Org. Chem.* **26**, 1805 (1961).

⁴⁸⁸ A. N. Kost and V. V. Ershov, *Vestn. Mosk. Univ.* No. 12, 115 (1955).

⁴⁸⁹ F. Blicke, *Org. Reactions* **1**, 319 (1942).

⁴⁹⁰ V. V. Ershov, A. N. Kost, and A. P. Terent'ev, *Zh. Obshch. Khim.* **27**, 258 (1957).

⁴⁹¹ A. N. Kost and V. V. Ershov, *Zh. Obshch. Khim.* **27**, 1072 (1957).

⁴⁹² A. N. Kost and V. V. Ershov, *Zh. Obshch. Khim.* **27**, 1722 (1957).

⁴⁹³ Yu. K. Yur'ev and N. K. Sadovaya, *Zh. Obshch. Khim.* **27**, 1587 (1957).

⁴⁹⁴ R. L. Hinman, R. D. Ellefson, and R. D. Campbell, *J. Am. Chem. Soc.* **82**, 3988 (1960).

⁴⁹⁵ A. N. Kost and I. I. Grandberg, *Zh. Obshch. Khim.* **26**, 1717 (1956).

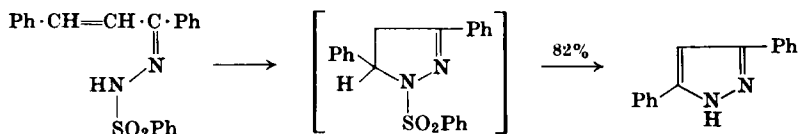
⁴⁹⁶ A. N. Kost, G. A. Golubeva, and I. I. Grandberg, *Zh. Obshch. Khim.* **26**, 1976 (1956).

⁴⁹⁷ A. N. Kost and I. I. Grandberg, *Zh. Obshch. Khim.* **26**, 2319 (1956).

⁴⁹⁸ A. N. Kost, I. I. Grandberg, and G. A. Golubeva, *Zh. Obshch. Khim.* **26**, 2604 (1956).

⁴⁹⁹ A. N. Kost, I. I. Grandberg, and E. B. Evreinova, *Zh. Obshch. Khim.* **28**, 512 (1958).

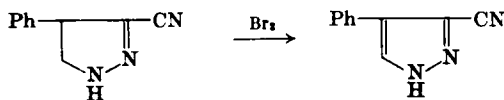
a molecule of amine.^{500,501} Here may be mentioned the unusual formation of 3,5-diphenylpyrazole from the benzenesulfonylhydrazone of benzalacetophenone by warming with sodium ethoxide in acetonitrile. The reaction evidently proceeds by cyclization to a pyrazoline and elimination of phenylsulfonic acid.^{502,502a}



The oxidation of pyrazolines by atmospheric oxygen usually gives rise to the formation of gaseous nitrogen and a complex mixture of ketones.⁵⁰³ When in contact with a porous material, spontaneous ignition sometimes occurs.⁴⁵² By this process, however, pyrazoles have been obtained in small yield in certain cases. Thus, 4-phenylpyrazoline on standing in air gives traces of 4-phenylpyrazole.⁵⁰⁴ Ethyl benzylidenacetate and phenylhydrazine are known to give 1,5-diphenyl-3-methyl-4-ethoxycarbonylpyrazole directly.⁵⁰⁵ This is clearly due to oxidation by means of the phenylhydrazine which is used in excess, since no free hydrogen is observed. If a pyrazoline has an electron-withdrawing substituent, it is more stable and may be oxidized to the pyrazole by the usual oxidizing agents.

1. Oxidation with Bromine

Pyrazoline-3- or -5-carboxylic acids, their derivatives, and the derivatives of the corresponding sulfonic acids are oxidized by bromine to the corresponding pyrazoles in yields of 50–75%.^{64, 153, 462, 464, 506}



⁵⁰⁰ N. H. Cromwell and H. Hoeksema, *J. Am. Chem. Soc.* **71**, 716 (1949).

⁵⁰¹ N. H. Cromwell and M. A. Craff, *J. Org. Chem.* **17**, 414 (1952).

⁵⁰² A. Dornow and W. Bartsch, *Ann.* **602**, 23 (1957).

^{502a} G. Ege, *Tetrahedron Letters*, No. 25, 1665 (1963).

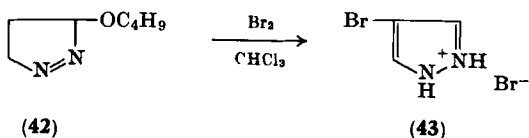
⁵⁰³ R. Locquin and R. Heilmann, *Bull. Soc. Chim. France* [4] **45**, 869 (1929).

⁵⁰⁴ E. Buchner and L. Perkel, *Ber.* **36**, 3774 (1903).

⁵⁰⁵ K. von Auwers and H. Mauss, *Ber.* **59**, 611 (1926).

⁵⁰⁶ S. Rondestvedt and R. Chang, *J. Am. Chem. Soc.* **77**, 6532 (1955).

The reaction has proceeded satisfactorily with one or two benzoyl groups present,^{153, 507} but a benzoyl group in position 1 has also been eliminated.¹⁵³ The oxidation proceeds similarly when position 4 is substituted.⁵⁰⁸ Pyrazoline itself and monoalkyl- and monoarylpyrazolines give the corresponding pyrazoles only in small yield on oxidation with bromine.^{509, 510} In the majority of cases bromination occurs together with oxidation, and often brominated products are the only ones isolated. Thus 1,3,5-triphenylpyrazoline yields a tribromide of unknown constitution.⁴⁹ The hydrobromide of 4-bromopyrazole (43) was obtained almost quantitatively from 3-butoxy- Δ^1 -pyrazoline (42).⁵¹¹ A mixture of 1,5-dimethylpyrazole and the 4-bromo compound



is obtained from 1,5-dimethylpyrazoline and bromine, and 1,3-dimethylpyrazoline yields a similar mixture.⁵¹² 1-Phenyl-3-methylpyrazoline forms only the bromine addition product.⁵¹³

2. The Use of Other Oxidizing Agents

The conversion of pyrazolines to pyrazoles has been accomplished successfully in a number of cases by using potassium permanganate.^{64, 507, 514} Side-chain double bonds are oxidized to carboxylic acids by this treatment.⁵¹⁵⁻⁵¹⁹ Amino groups should be protected.⁵²⁰

⁵⁰⁷ L. I. Smith and K. L. Howard, *J. Am. Chem. Soc.* **65**, 159 (1943).

⁵⁰⁸ E. P. Kohler and L. L. Steele, *J. Am. Chem. Soc.* **41**, 1093 (1919).

⁵⁰⁹ E. Fischer and O. Knoevenagel, *Ann.* **239**, 194 (1887).

⁵¹⁰ T. Curtius and F. Wirsing, *J. Prakt. Chem.* [2] **50**, 531 (1894).

⁵¹¹ I. A. D'yakonov, *Zh. Obshch. Khim.* **17**, 67 (1947).

⁵¹² F. Runge, H. J. Engelbrecht, and H. Franke, *Ber.* **88**, 533 (1955).

⁵¹³ G. B. Trener, *Monatsh.* **21**, 1111 (1900).

⁵¹⁴ H. Bauer and P. Vogel, *J. Prakt. Chem.* [2] **88**, 329 (1913).

⁵¹⁵ L. C. Raiford and L. B. Entrikin, *J. Am. Chem. Soc.* **55**, 1125 (1933).

⁵¹⁶ L. C. Raiford and R. H. Mauley, *J. Org. Chem.* **5**, 590 (1940).

⁵¹⁷ F. Staus, *Ber.* **51**, 1458 (1918).

⁵¹⁸ H. Bauer and H. Dieterle, *Ber.* **44**, 2697 (1911).

⁵¹⁹ H. R. Snyder, F. Verbanac, and D. B. Bright, *J. Am. Chem. Soc.* **73**, 3243 (1952).

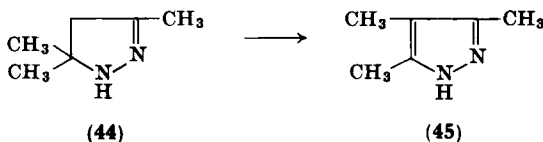
⁵²⁰ G. F. Duffin and J. D. Kendall, British Patent 743,505 (1956); *Chem. Abstr.* **50**, 16872 (1956).

Oxidation of Schiff's bases derived from 1-phenyl-3-aminopyrazoline gives 1-phenyl-3-arylamino-pyrazoles,⁴⁶⁹ the hetero ring and the arylidene group being oxidized simultaneously. See also Duffin and Kendall.⁵²⁰

With certain compounds, such as pyrazoline carboxylic acids and esters, potassium ferricyanide or silver nitrate has been used,⁵⁰⁹ and for those compounds unsubstituted on nitrogen, mercuric oxide or acetate.⁷⁶ Lead dioxide has been successful for the oxidation of 1-alkyl- and 1-arylpazolines,^{9, 76, 83} and in certain instances even chromic acid, but not hydrogen peroxide or silver oxide.⁷⁶ See also L. Smith⁵²¹ and Birkinshaw *et al.*⁵²²

3. Dehydrogenation of Pyrazolines with Sulfur or Selenium

The most general method of converting pyrazolines to pyrazoles is by dehydrogenation with sulfur or selenium, the former reagent being generally preferred. The reaction takes place at 200–220° and by it, alkyl- and arylpyrazolines, even when N-substituted, are smoothly dehydrogenated.^{62, 103, 105, 523–526} By this path, hydroxy-, acylamino-, and furylpyrazoles have been prepared. The reaction proceeded without complication when the benzene ring of arylpyrazolines was substituted with hydroxy, dialkylamino, alkoxy, or aryloxy groups, but pyrazolines with iodine or sulfur-containing groups could not be dehydrogenated satisfactorily.⁵²³ In the case of 3,5,5-trimethylpyrazoline (44) migration of a methyl group leads to the formation of a 1*H*-pyrazole (45) rather than a 4*H*-pyrazole.⁵²⁵



⁵²¹ L. Smith and W. Pings, *J. Org. Chem.* **2**, 23 (1937).

⁵²² J. H. Birkinshaw, A. E. Oxford, and H. Raistrick, *Biochem. J.* **30**, 394 (1936); *Chem. Abstr.* **30**, 4464 (1936).

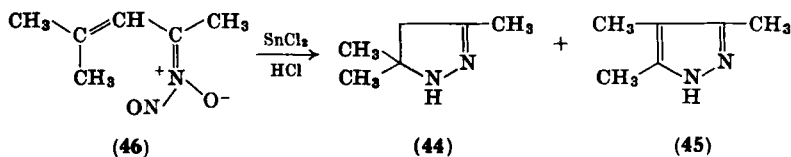
⁵²³ I. I. Grandberg, W.-P. Ting, and A. N. Kost, *Zh. Obshch. Khim.* **30**, 1373 (1960).

⁵²⁴ I. I. Grandberg, W.-P. Ting, A. N. Kost, and V. I. Kozlova, *Zh. Obshch. Khim.* **31**, 544 (1961).

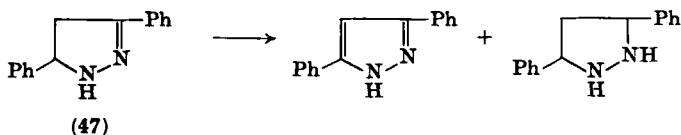
⁵²⁵ I. I. Grandberg, W.-P. Ting, and A. N. Kost, *Zh. Obshch. Khim.* **31**, 941 (1961).

⁵²⁶ I. I. Grandberg and A. N. Kost, Witness of Authorship in the U.S.S.R. No. 111905 (17.1.1958).

It is interesting that Fusco observed the formation of 3,4,5-trimethylpyrazole (45), in addition to the expected 3,5,5-trimethylpyrazoline (44), when the *N*-oxide (46) was reduced with stannous chloride and hydrochloric acid.⁵²⁷



Catalytic dehydrogenation of pyrazolines has been little studied so far. Platinum catalyzes the conversion of Δ^2 -pyrazolines to the Δ^1 -isomers and the subsequent breakdown to form cyclopropanes and olefins.⁵²⁸ Attempts to dehydrogenate 1-benzoyl-3-methoxycarbonyl-4-methylpyrazoline over platinum or palladium were unsuccessful.¹⁵³ When heated with platinum black under various conditions, 3,4-dibenzoylpyrazoline gave only traces of dehydrogenated material.⁵⁰⁷ Recently it has been shown, however, that 3,5-diphenylpyrazoline (47), on heating with colloidal platinum, undergoes disproportionation to the corresponding pyrazole and pyrazolidine.⁵²⁹ If the



3-position in the pyrazoline is unsubstituted, as in 48, then under the same conditions rearrangement similar to a second-order Beckmann rearrangement takes place, and a β -aminonitrile (49) is formed.⁵³⁰

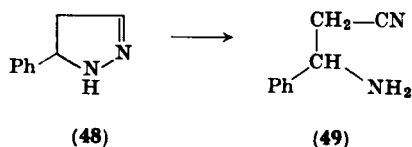
Concerning the formation of pyrazoles from acyclic compounds, see

⁵²⁷ R. Fusco and F. D'Alo, *Atti Accad. Ital., Rend. Classe Sci. Fis., Mat. Nat.* [7] **3**, 113 (1941); *Chem. Abstr.* **38**, 2928 (1944).

⁵²⁸ V. M. Rodionov and N. G. Yartseva, in "Reactions and Methods of Investigation of Organic Compounds," Vol. 1, p. 7. Goskhimisdats, 1951.

⁵²⁹ G. A. Golubeva, "Hydrogenation and the Catalytic Cleavage of Nitrogen-Nitrogen Links in Pyrazolines," Candidate's Dissertation, Moscow University (1962).

⁵³⁰ A. N. Kost, G. A. Golubeva, A. P. Terent'ev, and I. I. Grandberg, *Dokl. Akad. Nauk SSSR* **144**, 359 (1962).

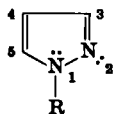


Kost and Sagitullin,⁵³¹ Fridel and Combes,⁵³² Domnin,^{533, 534} and Kauffmann^{534a} For the synthesis of pyrazoles consequent on the formation of an N—N link, see Belov,⁴⁵ Fowden,¹³⁰ Brian *et al.*,³⁰⁰ and others.^{306, 535, 536} A number of pyrazoles have been prepared from pyrazolinones; see, for example, Michaelis and Lachwitz⁵³⁷ or Mustafa and co-workers.^{537a}

IV. Chemical Properties of the Pyrazole Nucleus

A. GENERAL

The three carbon atoms and one nitrogen atom of the nucleus contribute four π -electrons, and the nitrogen atom in position 1, which is not involved in double bond formation, donates its electron pair, thus creating an aromatic sextet of π -electrons. At the same time the 1-position nitrogen loses its basic properties, although the nitrogen atom in position 2 remains weakly basic.



The 1-nitrogen atom of N-substituted pyrazoles contributes its electron pair to the formation of an aromatic sextet, and thus assumes

⁵³¹ A. N. Kost and R. S. Satullin, *Zh. Obshch. Khim.* **33**, 237 (1963).

⁵³² C. Fridel and A. Combes, *Bull. Soc. Chim. France* [3] **11**, 115 (1894).

⁵³³ N. A. Domnin, V. N. Dyurnbaum, and V. A. Cherkasova, *Zh. Obshch. Khim.* **28**, 1469 (1958).

⁵³⁴ N. A. Domnin, in "Theoretical Problems Concerning the Structure of Organic Compounds," p. 107. Leningrad Univ. Press, 1960.

^{534a} T. Kauffmann and H. Müller, *Ber.* **96**, 2206 (1963).

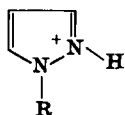
⁵³⁵ R. A. Abramovitch, Y. Ahmad, and D. Newman, *Tetrahedron Letters* No. 21 752 (1961).

⁵³⁶ R. A. Abramovitch and K. A. H. Adams, *Can. J. Chem.* **39**, 2516 (1961).

⁵³⁷ A. Michaelis and A. Lachwitz, *Ber.* **43**, 2107 (1910).

^{537a} A. Mustafa, W. Asker, A. F. Shalaby, and Z. Selim, *J. Org. Chem.* **26**, 1779 (1961).

some cationic character which is balanced by the slight anionic character assumed by the remaining ring atoms. The second nitrogen atom in the ring (like that in pyridine and in contrast to pyrrole) contributes two electrons in the formation of σ -bonds and one electron toward the aromatic sextet, and retains an electron pair which gives it basic properties. Because of the electrostatic effect of the two nitrogen nuclei of greater nuclear charge than carbon, there is a reduction in charge density at positions 3 and 5 of the ring, and consequently electrophilic attack at these positions is less likely. The carbon atom at position 4 retains its anionic character and this is the site of electrophilic attack. The electrostatic effect is greatly enhanced in acid media, in which pyrazole exists mainly as the cation; hence electrophilic attack, which takes place readily in neutral or basic media, is hindered in acid. The general pattern of the distribution of



electron density is somewhat complicated for pyrazoles with free N—H groups. In these cases one must take into account the equivalence of the two nitrogen atoms and hence the sharing of the hydrogen atoms, at any rate in the dimer. In the idealized case the two nitrogen atoms contribute electrons equally in the creation of an aromatic system, and each in its turn reduces the anionic character of positions 3 and 5 by an electrostatic effect. Thus these positions in pyrazoles resemble positions 2 and 6 in pyridine, and are not susceptible to electrophilic attack but are attacked more readily by nucleophiles. In 1-substituted pyrazoles, nucleophilic attack occurs mostly at the 5-position. A specific comparison between the reactivity of pyrazoles and other aromatic systems has not been reported. The reactivity of the 4-position in electrophilic substitutions is probably intermediate between the reactivities of benzene and phenol, whereas the pyrazole cation is less reactive than benzene.

The hydrogen atoms of the methyl and carboxyl groups of 1-phenyl-3-methylpyrazole-5-carboxylic acid are replaced by deuterium under mildly alkaline conditions.⁵³⁸ No other example of hydrogen exchange in a methylpyrazole seems to have been recorded.

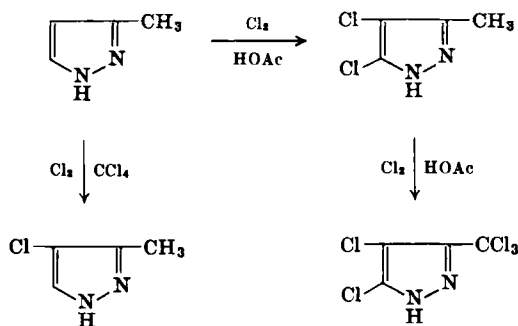
⁵³⁸ H. Erlenmeyer, H. M. Weber, and P. Wiessner, *Helv. Chim. Acta* **21**, 1017 (1938).

B. ELECTROPHILIC SUBSTITUTION REACTIONS

Knorr and Buchner, who discovered pyrazole, noticed that, like other aromatic compounds, it had a particularly stable nucleus and a tendency to undergo substitution.^{64, 77, 208} As mentioned above, this takes place principally in the 4-position.

1. Chlorination

Chlorination of pyrazoles in neutral or weakly acid media leads to 4-chloropyrazoles. Successful chlorinating agents are sulfuryl chloride^{86, 280, 286, 539, 540} or phosphorus pentachloride^{60, 537, 541, 542} in neutral solution at low temperatures. Recently the successful use of mixtures of hydrogen chloride and peracetic or performic acids has been described.^{74, 543} Hüttel, Schaefer, and Welzel⁵⁴⁴ established that free chlorine in weakly polar solvents reacted with 3-methylpyrazole to give 3-methyl-4-chloropyrazole. In acetic acid solution the reaction proceeded further to 3-methyl-4,5-dichloro- and then 3-trichloro-methyl-4,5-dichloro-pyrazole.



Only the methyl groups in positions 3 and 5 of 3,4,5-trimethylpyrazole are chlorinated, and not that in position 4 where the electron density

⁵³⁹ G. Mazzara and A. Borgo, *Gazz. Chim. Ital.* **36**, Part II, 348 (1906).

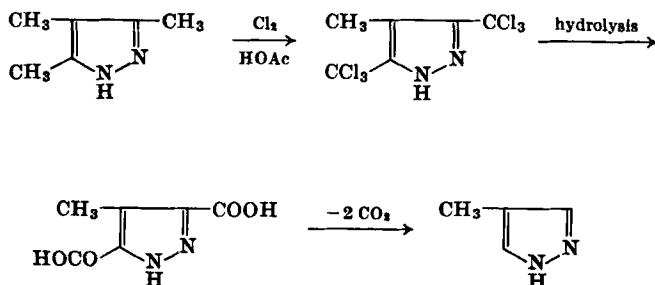
⁵⁴⁰ G. Mazzara and A. Borgo, *Atti R. Accad. Lincei* Part I, 704 (1906); *Chem. Zentr.* **II**, 684 (1906).

⁵⁴¹ A. Michaelis, *Ann.* **385**, 1 (1911).

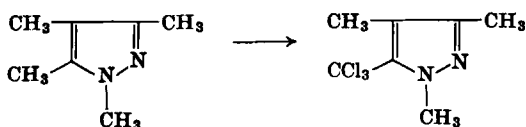
⁵⁴² I. I. Grandberg, *Zh. Obshch. Khim.* **31**, 548 (1961).

⁵⁴³ M. Lipp, F. Dallacker, and S. Munnes, *Ann.* **618**, 110 (1958).

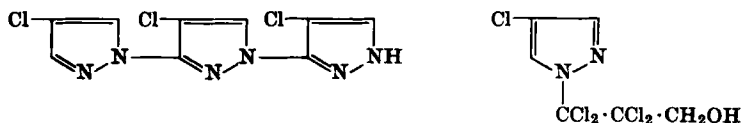
⁵⁴⁴ R. Hüttel, O. Schäfer, and G. Welzel, *Ann.* **598**, 186 (1956).



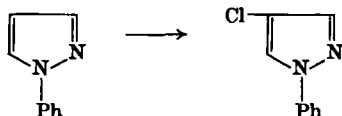
is greatest. The most active methyl group of 1,3,4,5-tetramethylpyrazole is that in position 5.⁵⁴⁴ The direct chlorination of pyrazole



itself is complicated. Besides 4-chloropyrazole, polymeric substances were observed,⁵⁴⁴ to which the authors attribute the following structures:



Halogenation of phenylpyrazoles always takes place in the pyrazole ring to give 4-halogeno derivatives.^{60, 76, 266, 350, 541, 545-554}



⁵⁴⁵ A. Michaelis and W. Rassmann, *Ann.* **352**, 158 (1907).

⁵⁴⁶ O. Severini, *Atti accad. naz. Lincei* [5] **1**, Part II, 391 (1892); *Chem. Zentr.* **64** (part I), 255 (1893).

⁵⁴⁷ L. Balbiano, *Gazz. Chim. Ital.* **19**, 128 (1889).

⁵⁴⁸ O. Severini, *Gazz. Chim. Ital.* **23**, Part I, 284 (1893).

⁵⁴⁹ A. Michaelis and R. Pasternack, *Ber.* **32**, 2398 (1899).

⁵⁵⁰ A. Michaelis and H. Behn, *Ber.* **33**, 2603 (1900).

⁵⁵¹ A. Michaelis and C. Mayer, *Ann.* **338**, 273 (1905).

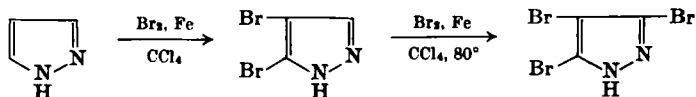
⁵⁵² A. Michaelis and C. Käding, *Ann.* **373**, 202 (1910).

⁵⁵³ W. Dieckmann and L. Platz, *Ber.* **37**, 4638 (1904).

⁵⁵⁴ S. Olsen, L. Kühn, and G. Friedberg, *Ber.* **81**, 540 (1948).

2. Bromination

Bromination in the 4-position is the most facile reaction of all pyrazole electrophilic substitutions. Aqueous bromine is usually employed,^{208, 286, 555, 556} or bromine in neutral solvents,^{208, 557-574} or else hypobromous acid⁵⁶² or such agents as *N*-bromosuccinimide.⁵⁶⁵ During bromination in aqueous solution^{543, 566} it is usual to neutralize the hydrobromic acid formed by the addition of an equimolar quantity of sodium acetate, but this is by no means necessary. Bromination in the presence of a catalyst such as iron may result in the introduction of two or even three bromine atoms,⁵⁵⁷ although Buchner and Fritsche⁶⁴ earlier considered the introduction of more than one impossible. See also Michaelis.⁵⁴¹ The action of bromine on 1,3-



dimethylpyrazole was reported to give a compound to which the structure 1,3-dimethyl-4,5-dibromopyrazole (**50**) was assigned,⁵⁴⁷ but this work could not be repeated.⁵⁵⁷ It was also reported that 1-phenyl-4-bromo-3-methylpyrazole and the corresponding *p*-bromophenyl

⁵⁵⁵ E. Buchner, *Ann.* **273**, 214 (1893).

⁵⁵⁶ K. Boehr, *J. Prakt. Chem.* [2] **116**, 93 (1927).

⁵⁵⁷ R. Hüttel, H. Wagner, and P. Jochum, *Ann.* **593**, 179 (1955).

⁵⁵⁸ L. Knorr, *Ber.* **28**, 714 (1895).

⁵⁵⁹ S. Veibel and N. H. Arnfred, *Acta Chem. Scand.* **2**, 914 (1948).

⁵⁶⁰ C. A. Rojahn, *Ber.* **55**, 2965 (1922).

⁵⁶¹ H. A. D. Jowett and C. E. Potter, *J. Chem. Soc.* **83**, 469 (1903).

⁵⁶² C. Musante, *Gazz. Chim. Ital.* **78**, 178 (1948).

⁵⁶³ K. von Auwers and F. Niemeyer, *J. Prakt. Chem.* [2] **110**, 153 (1925).

⁵⁶⁴ S. Veibel and N. H. Arnfred, *Acta Chem. Scand.* **2**, 921 (1948).

⁵⁶⁵ K. Liegler, A. Späth, F. Schaaf, W. Schumann, and E. Winkelmann, *Ann.* **551**, 80 (1942).

⁵⁶⁶ I. I. Grandberg and A. N. Kost, *Zh. Obshch. Khim.* **32**, 874 (1962).

⁵⁶⁷ A. Michaelis and C. Schwabe, *Ber.* **33**, 2607 (1900).

⁵⁶⁸ I. L. Finar and D. B. Miller, *J. Chem. Soc.* **1961**, 2769.

⁵⁶⁹ L. Balbiano, *Gazz. Chim. Ital.* **75**, 121 (1945).

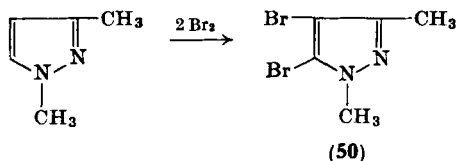
⁵⁷⁰ L. Knorr and J. Macdonald, *Ann.* **279**, 217 (1894).

⁵⁷¹ R. Hüttel, O. Schäfer, and P. Jochum, *Ann.* **593**, 200 (1955).

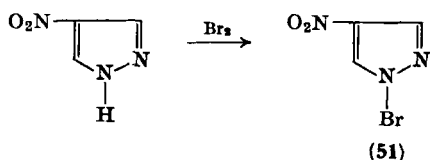
⁵⁷² G. T. Morgan and I. Ackerman, *J. Chem. Soc.* **123**, 1317 (1923).

⁵⁷³ D. H. Derbyshire and W. A. Waters, *J. Chem. Soc.* **1950**, 3694.

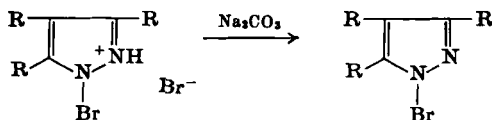
⁵⁷⁴ K. von Auwers and H. Hollmann, *Ber.* **59**, 601 (1926).



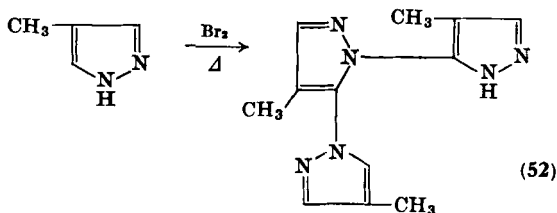
compound gave 4,5-dibromo derivatives on bromination without a catalyst.^{550, 567} However, Finar⁵⁶⁸ showed that the dibromo compound obtained from 1-phenyl-3-methylpyrazole is not the 4,5-dibromo derivative but 1-*p*-bromophenyl-4-bromo-3-methylpyrazole. Likewise, 1-phenylpyrazole was reported to give a tribromo derivative, but probably one bromine atom is substituted in the benzene ring. The hydrogen atom attached to nitrogen may be replaced by bromine, though not by chlorine. Thus pyrazoles with electron-donating groups in the 4-position form 1-bromo derivatives (e.g., **51**) on reaction with bromine.⁵⁵⁷ The colored compounds formed by the action of excess



bromine on pyrazoles, and considered earlier as perbromides, are in fact pyrazole salts which react with weak alkalis to give 1-bromopyrazoles. A bromine atom in position 1 is comparatively mobile and

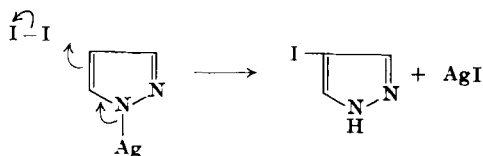


such compounds resemble *N*-bromosuccinimide. The action of bromine on 4-methylpyrazole at elevated temperatures gives rise to complex condensation products (e.g., **52**).⁵⁵⁷ Such reactions do not occur when electron-withdrawing groups are present in the ring.⁵⁵⁷

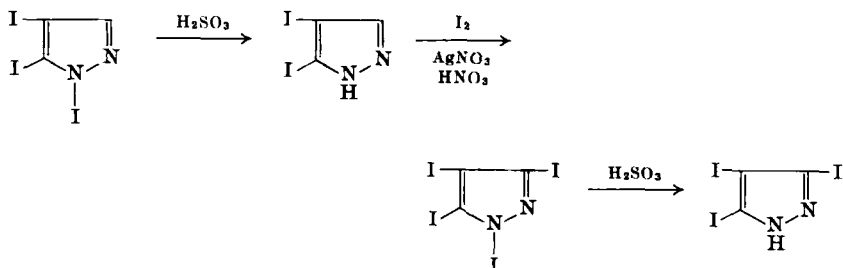


3. Iodination

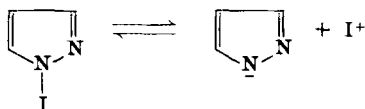
Buchner and Fritsche initially considered that the hydrogen atoms of pyrazole could not be replaced by iodine.⁶⁴ Buchner himself, however, later obtained 4-iodopyrazole by the action of iodine solution on the silver salt of pyrazole.⁵⁵⁵



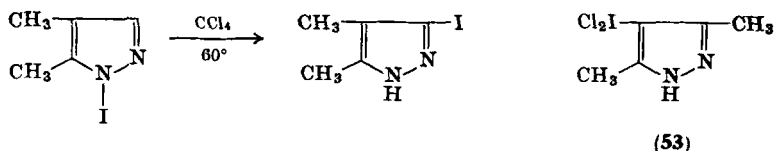
A more detailed study of the reaction showed that direct iodination takes place when the hydriodic acid formed in the reaction is neutralized by the addition of alkali,²⁸⁰ hypiodous acid,^{559, 570} or sodium acetate.^{571, 572} In order to introduce a second iodine atom, Derbyshire and Waters⁵⁷³ used excess iodine in the presence of silver nitrate and nitric acid and obtained 1,4,5-triiodopyrazole. The iodine atom in the 1-position was readily removed by the action of sulfur dioxide or hydriodic acid. Further treatment of 4,5-diiodopyrazole gave 1,3,4,5-tetraiodopyrazole and hence 3,4,5-triiodopyrazole. Methylation of the nitrogen atom facilitates iodination of the ring.⁵⁷¹



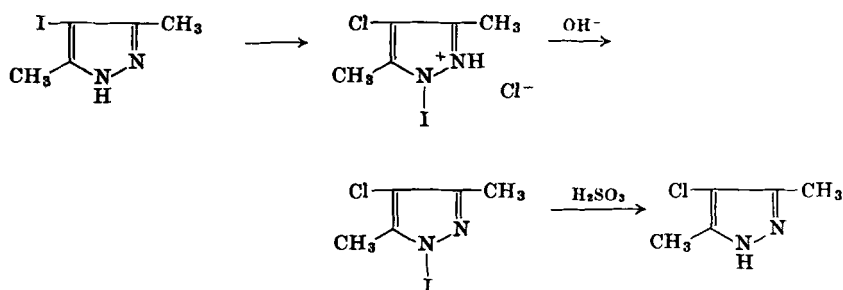
N-Iodopyrazoles are quite stable compounds and can be kept for some time without change. This is due to the fact that the iodine cation is more stable than those of the other halogens. The formation of an iodine cation from 1-iodo-4,5-dimethylpyrazole is so facile that



the compound readily undergoes rearrangement via electrophilic substitution in the ring.⁵⁷¹



Unlike chlorine and bromine, neither iodine itself nor hypiodous acid is capable of causing oxidative condensation to form compounds containing more than one pyrazole ring. In 1925, chlorine and bromine with 4-iodo-3,5-dimethylpyrazole were shown by Morgan and Ackerman⁵⁷² to yield addition products to which they ascribed structures such as 53. All their attempts to convert the products to iodoso or iodo compounds were unsuccessful. Later, Hüttel and co-workers showed that in this process the more reactive halogens expelled iodine from the 4-position, initially forming 1-iodo derivatives, which by mild reduction could be converted into 4-chloro- or 4-bromo-3,5-dimethylpyrazole. Iodination of pyrazoles is further described.^{77, 440, 527, 546, 574a} For the halogenation of pyrazole carboxylic acids, see von Auwers,^{153, 574, 575} and others.⁵⁷⁶⁻⁵⁷⁸



4. Nitration

Pyrazoles require more severe nitration conditions than benzene, due to the fact that the pyrazole cation which is formed is more

^{574a} J. D. Vangham, D. G. Lambert, V. L. Vangham, *J. Am. Chem. Soc.* **86**, 2857 (1964).

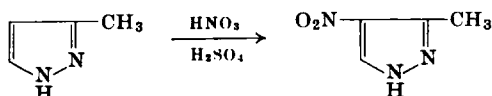
⁵⁷⁵ K. von Auwers and T. Mausolf, *Ber.* **60**, 1732 (1927).

⁵⁷⁶ L. Balbiano and O. Severini, *Gazz. Chim. Ital.* **23**, Part I, 354 (1893).

⁵⁷⁷ C. A. Rojahn and A. Seitz, *Ann.* **437**, 308 (1924).

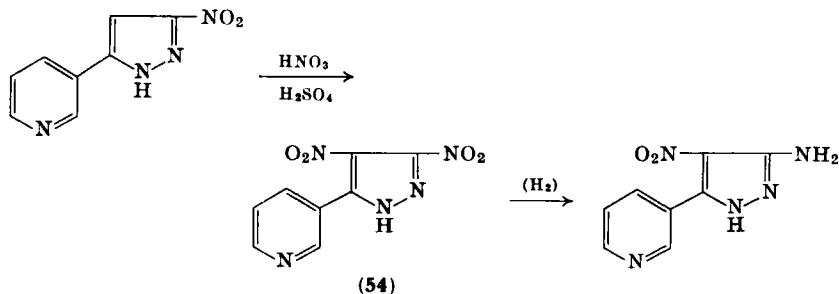
⁵⁷⁸ C. A. Rojahn and H. E. Kühling, *Arch. Pharm.* **264**, 342 (1926).

resistant to electrophilic attack than pyrazole itself. Thus Knorr, in nitrating 3-methylpyrazole, used nitrating mixture on a water bath for 5 hours.²⁰⁸ As 1-phenylpyrazoles have scarcely any basic properties



and only reluctantly form pyrazole cations, nitration takes place under the milder conditions of nitric acid at 20°, whereupon nitro groups are introduced both in the 4-position of the pyrazole ring and the *para* position of the benzene ring.^{159, 567, 579-581, 581a, 581b} See, however, Ridi *et al.*⁵⁸² Similar results are obtained with 3-phenylpyrazoles.⁵⁸³⁻⁵⁸⁵

The introduction of other electron-withdrawing or -donating groups enables nitration of one or another of the rings to be accomplished selectively. Thus, 1-phenyl-3-methylpyrazole is nitrated only in the pyrazole ring, whereas 1-phenylpyrazole-3-carboxylic acid nitrates only in the *para* position of the benzene ring.⁵⁸⁶ The only dinitropyrazole recorded was obtained from 3-nitro-5-(pyrid-3-yl)-pyrazole.^{249, 587} In the nitration product (54) the nitro group at



⁵⁷⁹ A. Michaelis and Th. Sudendorf, *Ber.* **33**, 2615 (1900).

⁵⁸⁰ L. Knorr and H. Laubmann, *Ber.* **22**, 172 (1889).

⁵⁸¹ I. L. Finar and R. J. Hurlock, *J. Chem. Soc.* **1957**, 3024.

^{581a} M. A. Khan, B. M. Lynch, and Y. Y. Hung, *Canad. J. Chem.* **41**, 1540 (1963).

^{581b} M. L. Brian and H. Lung, *Canad. J. Chem.* **42**, 1605 (1964).

⁵⁸² M. Ridi, P. Papini, and S. Checchi, *Gazz. Chim. Ital.* **92**, 209 (1962).

⁵⁸³ D. Dal Monte Casoni, *Ann. Chim. (Rome)* **48**, 783 (1958).

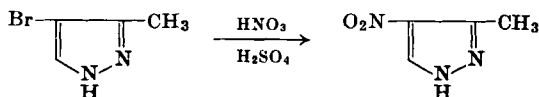
⁵⁸⁴ A. Michaelis, *Ann.* **378**, 293 (1910).

⁵⁸⁵ C. Musante, *Farmaco, Sci. Tec. (Pavia)* **6**, 32 (1951); *Chem. Abstr.* **45**, 5879 (1951).

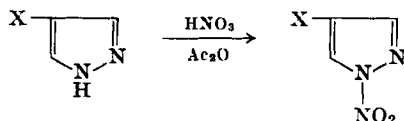
⁵⁸⁶ D. Dal Monte Casoni, *Gazz. Chim. Ital.* **89**, 1539 (1959).

⁵⁸⁷ H. Lund, *J. Chem. Soc.* **1935**, 418.

position 3 could be reduced selectively.⁵⁸⁷ For the nitration of other pyrazoles see Buchner *et al.*,⁶⁴ Musante,⁵⁸⁵ and others.⁵⁸⁸⁻⁵⁹² Musante⁵⁶² has described the expulsion of the bromine atom during nitration of 4-bromo-3-methylpyrazole. Treatment of pyrazoles with



free N—H groups with a mixture of acetic anhydride and fuming nitric acid in the cold gives 1-nitropyrazoles. The presence in the



molecule of either strongly electron-withdrawing or -donating groups lowers the yield. The best yields are obtained from 4-halogenopyrazoles.⁵⁹³

5. Nitrosation

Direct nitrosation of pyrazoles cannot be accomplished: to obtain 4-nitrosopyrazoles, β -diketones are nitrosated and then treated with hydrazine or a hydrazine derivative.⁵⁹⁴ Nitrosation of 3- and 5-hydroxypyrazoles (pyrazolinones) takes place readily in the 4-position,⁵⁹⁵ but 4-hydroxypyrazoles yield 5-nitroso derivatives.⁵⁹⁶ The following compounds are also nitrosated at the 4-position: 1,3-dimethyl-5-methylthiopyrazole,⁵⁴² 3-methyl-5-ethoxypyrazole,⁵⁹⁷ and 1-phenyl-3-methyl-5-aminopyrazole (55),^{598,599} but in the last case diazotization predominates.

⁵⁸⁸ R. Hüttel, F. Buchele, and P. Jochum, *Ber.* **88**, 1577 (1955).

⁵⁸⁹ G. Marchetti, *Gazz. Chim. Ital.* **22**, Part II, 351 (1892).

⁵⁹⁰ L. Knorr, *Ann.* **279**, 232 (1894).

⁵⁹¹ R. Rothenburg, *Ber.* **27**, 956 (1894).

⁵⁹² C. Musante, *Gazz. Chim. Ital.* **75**, 121 (1945).

⁵⁹³ R. Hüttel and F. Büchele, *Ber.* **88**, 1586 (1955).

⁵⁹⁴ L. Wolff, *Ann.* **325**, 129 (1902).

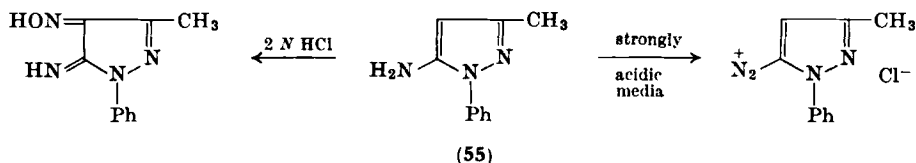
⁵⁹⁵ V. Hovorka and L. Šucha, *Collection Czech. Chem. Commun.* **25**, 60 (1960).

⁵⁹⁶ L. Wolff and A. Lüttringhaus, *Ann.* **313**, 6 (1900).

⁵⁹⁷ H. J. Backer and W. Meijer, *Rec. Trav. Chim.* **45**, 431 (1926).

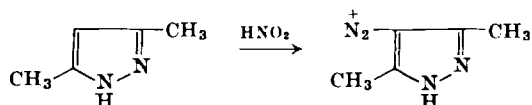
⁵⁹⁸ A. Michaelis and A. Schäfer, *Ann.* **407**, 233 (1915).

⁵⁹⁹ E. Mohr, *J. Prakt. Chem.* [2] **79**, 16 (1909).



In a strongly acidic medium the pyrazole nucleus exists as a cation from which the hydrogen atom at position 4 cannot be displaced by electrophilic substitution such as nitrosation. In a less acidic medium the weakly basic 2-nitrogen atom of a 1-phenylpyrazole is not protonated, and the pyrazole activated by the electron-donating amino group is readily nitrosated in position 4. See also Grandberg and Klyuchko.⁶⁰⁰ Nitrosation in the 4-position of 1-phenyl-3-methyl-5-sulfanilamidopyrazole occurred successfully.⁶⁰¹

Recently it was shown that, in a buffered solution where the pyrazole cation was in equilibrium with basic pyrazole, a diazonium group could be directly substituted into the 4-position of 3,5-dimethylpyrazole by nitrous acid,^{602, 602a} in the same way that this group had been introduced into phenols.⁶⁰³ For the properties of 3-, 4-, and 5-diazopyrazoles see Knorr,⁷⁷ Alberti,³¹⁸ Fusco,⁵²⁷ and others.^{571, 572, 597, 604-610}



6. Sulfonation

As with nitration, sulfonation proceeds only with difficulty due to cation formation. Knorr sulfonated 3-methylpyrazole in the 4-position by heating it at 100° for 6 hours in 20% oleum.²⁰⁸ Pyrazole sulfonic

⁶⁰⁰ I. I. Grandberg and G. V. Klyuchko, *Zh. Obshch. Khim.* **32**, 1898 (1962).

⁶⁰¹ M. Guarneri and L. Duda, *Ann. Chim. (Rome)* **49**, 958 (1959).

⁶⁰² H. P. Patel, J. M. Tedder, and B. Webster, *Chem. Ind. (London)* **1961**, 1163.

^{602a} H. P. Patel and J. M. Tedder, *J. Chem. Soc.* **1963**, 4589.

⁶⁰³ J. M. Tedder and G. Theaker, *J. Chem. Soc.* **1958**, 2573.

⁶⁰⁴ D. G. Farnum and P. Yates, *Chem. Ind. (London)* **1960**, 659.

⁶⁰⁵ E. Mohr, *J. Prakt. Chem.* [2] **90**, 223 (1914).

⁶⁰⁶ C. Iwanoff, *Ber.* **87**, 1600 (1954).

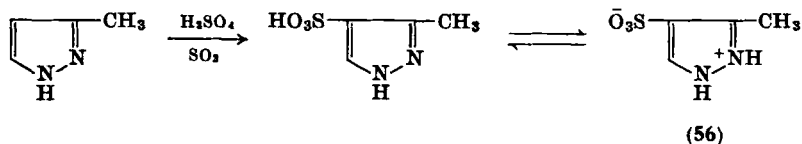
⁶⁰⁷ W. E. Parham and J. M. Aldre, *J. Org. Chem.* **25**, 1259 (1960).

⁶⁰⁸ H. Reimlinger, A. van Overstraeten, and H. G. Viehe, *Ber.* **94**, 1036 (1961).

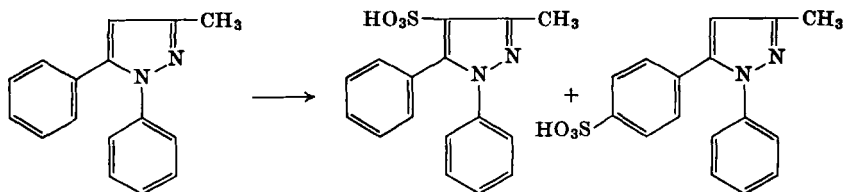
⁶⁰⁹ D. G. Farnum and P. Yates, *J. Am. Chem. Soc.* **84**, 1399 (1962).

⁶¹⁰ A. Dornow and E. Hinz, *Ber.* **91**, 1834 (1958).

acids are amphoteric compounds though predominantly acidic. They probably exist as betaines (e.g., 56) and are obtained under conditions such as those used by Knorr. It is interesting to note that sulfonation of 3-methyl-1,5-diphenylpyrazole takes place at position 4 of the



pyrazole ring and at the *para* position of the 5-phenyl group, not in the 1-phenyl group as was earlier reported. Thus the conjugation between the pyrazole ring and a substituent phenyl group is seen to depend on the position of the latter.⁶¹¹ For the sulfonation of pyrazoles see also Buchner,⁶⁴ Knorr,⁷⁷ *et al.*^{572, 612}



7. Azo Coupling

Pyrazole itself does not couple with diazonium salts under normal conditions, but the presence of electron-donating groups facilitates this reaction. Thus, 3- and 5-hydroxypyrazoles readily couple in the 4-position (for example see Rosengarten¹³⁴ and Knorr⁶¹³), and 4-hydroxypyrazole in position 5.⁵⁹⁶ Azo coupling occurs analogously in the 4-position of 5-aminopyrazoles.^{598, 599, 614, 615}

8. Mercuration

In the earliest papers on pyrazole chemistry it was noted that pyrazoles, whether substituted on nitrogen or not, react with mercury

⁶¹¹ L. Knorr and F. Schall, *Ann.* **279**, 230 (1894).

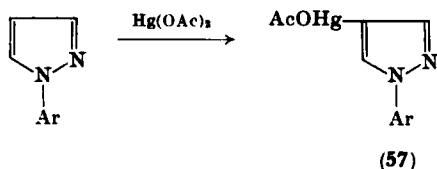
⁶¹² W. Barry, *J. Chem. Soc.* **1961**, 3851.

⁶¹³ L. Knorr, *Ber.* **21**, 1201 (1888).

⁶¹⁴ E. C. Taylor, J. W. Barton, and T. S. Osdene, *J. Am. Chem. Soc.* **80**, 421 (1958).

⁶¹⁵ M. Guarneri and L. Duda, *Ann. Chim. (Rome)* **51**, 446 (1961).

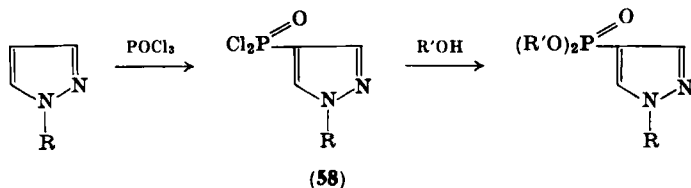
salts to give compounds of varied composition.^{64, 116, 570, 616-618} Finar^{219, 350} showed that 1-arylpyrazoles give 4-acetoxymercury derivatives (57) with mercuric acetate, although the structure of the products obtained was not proved rigorously.



Grandberg, Kost, and Zheltikova¹⁰⁸ have shown recently that mercuric salts mercurate pyrazoles in the 4-position and also give other complexes with variable quantities of the mercuric salts. The proportion of mercuric salt bound as a complex depends on the basicity of the starting pyrazole. The mercuric group in mercurated pyrazoles behaves in a variety of reactions just as phenyl mercuric chloride.^{108, 219, 350}

9. Phosphorylation

Phosphorus oxychloride at 230–250° phosphorylates 1-substituted pyrazoles in the 4-position. By the action of alcohols, the phosphonodichlorides (58) are converted into esters.⁶¹⁹ Phosphorylation here is presumably an electrophilic substitution.



10. Thiénylation

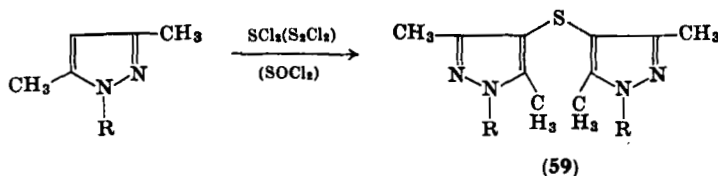
In spite of their reluctance to undergo electrophilic substitution, pyrazole hydrochlorides react under comparatively mild conditions (80–100°) with sulfur dichloride, sulfur monochloride, and even thionyl chloride to give sulfides (59).⁵⁴⁴ Earlier it was erroneously

⁶¹⁶ G. D. Rosengarten, *Ann.* **279**, 238 (1894).

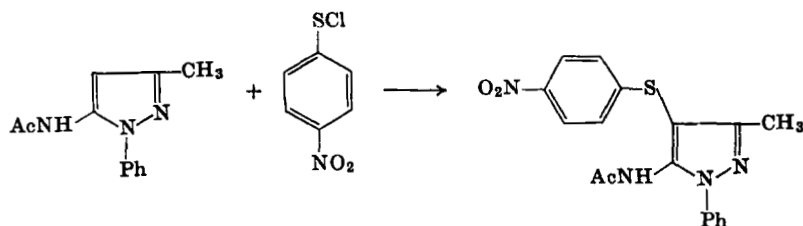
⁶¹⁷ W. Schrauth and H. Bauerschmidt, *Ber.* **47**, 2736 (1914).

⁶¹⁸ B. Oettinger, *Ann.* **279**, 245 (1894).

⁶¹⁹ I. I. Grandberg and A. N. Kost, *Zh. Obshch. Khim.* **31**, 129 (1961).

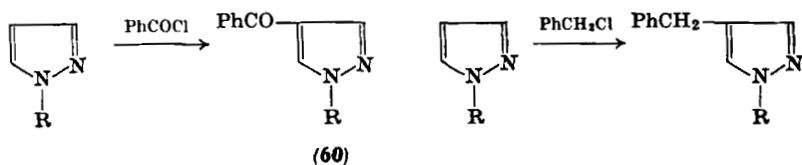


stated that 1-phenylpyrazole formed the 4,4'-dipyrazolylsulfoxide⁶²⁰; the product is in fact a sulfide.⁵⁴⁴ Amino groups facilitate electrophilic substitution and acylated 5-aminopyrazoles react with *p*-nitrobenzenesulfonylchloride.⁶²¹



11. Acylation and Alkylation

The Friedel-Crafts reaction has limited application in pyrazole chemistry, as the acyl group can be introduced only in the 4-position. The reaction is easier with 1-arylpyrazoles which are less inclined to form pyrazole cations.^{622, 623} Heating N-substituted pyrazoles with benzoyl chloride at 200–230° for some hours gives high yields of 4-benzoylpyrazoles (60) even in the absence of catalysts.^{46, 505, 547, 624, 625}



⁶²⁰ I. L. Finar and G. H. Lord, *J. Chem. Soc.* **1959**, 1818.

⁶²¹ S. Checchi, M. Ridi, and P. Papini, *Gazz. Chim. Ital.* **85**, 1558 (1955).

⁶²² A. Michaelis and C. A. Rojahn, *Ber.* **50**, 737 (1917).

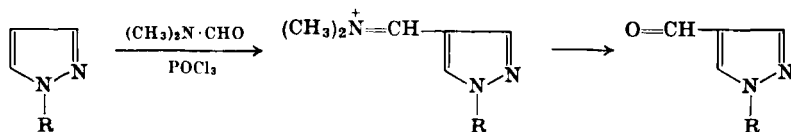
⁶²³ C. A. Rojahn, *Ber.* **55**, 291 (1922).

⁶²⁴ L. Balbiano and J. Marchetti, *Atti accad. naz. Lincei*, Part I, 398 (1893); *Ber.* **26R**, 599 (1893).

⁶²⁵ O. Severini, *Atti accad. naz. Lincei* 377, Part II (1891); *Ber.* **25R**, 164 (1892).

Benzylation of N-substituted pyrazoles proceeds similarly in the 4-position in high yield.⁶²⁶ Earlier the reaction was reported to fail with pyrazoles unsubstituted or alkyl-substituted in the 1-position.⁶²⁷ However, Grandberg and co-workers have recently shown that in the presence of a large excess of aluminum chloride the acylation of a variety of pyrazoles may be accomplished.^{68, 109}

A further example of electrophilic substitution is the synthesis of pyrazole aldehydes by formylation with dimethylformamide.^{620, 628}



Poorer results were obtained when methylformanilide was used in place of dimethylformamide.⁶²⁹ Formylation was unsuccessful with pyrazoles acylated or unsubstituted in the 1-position.^{620, 630}

Concerning the properties of pyrazole aldehydes and ketones, see Borsche and Hahn,¹⁵⁴ Wolff,¹⁹⁵ Panizzi,²⁶⁸ and others.^{350, 356, 357, 380, 450, 458, 473, 478, 480, 620, 623, 628, 631-642} For *N*-acylation and *N*-alkylation of pyrazoles see Section IV, D, 1 and 2. For the acylation of the functional groups of hydroxy- and amino-pyrazoles see, for example, Gysin⁴⁰ and Wahlberg.⁶⁴³

⁶²⁶ I. I. Grandberg and A. N. Kost, *Zh. Obshch. Khim.* **30**, 2942 (1960).

⁶²⁷ E. Ochiai, *J. Pharm. Soc. Japan* **60**, 164 (1939); *Chem. Abstr.* **34**, 5450 (1940).

⁶²⁸ I. L. Finar and M. Manning, *J. Chem. Soc.* **1961**, 2733.

⁶²⁹ I. L. Finar and L. Godfrei, *J. Chem. Soc.* **1954**, 2294.

⁶³⁰ F. Fichter and H. de Montmollin, *Helv. Chim. Acta* **5**, 256 (1922).

⁶³¹ T. W. Solomons and F. W. Fowler, *Chem. Ind. (London)* **1963**, 1462.

⁶³² I. L. Finar and G. H. Lord, *J. Chem. Soc.* **1957**, 3314.

⁶³³ R. H. Eastman and F. L. Detert, *J. Am. Chem. Soc.* **70**, 962 (1948).

⁶³⁴ C. A. Rojahn and A. Seitz, *Ann.* **437**, 297 (1924).

⁶³⁵ C. A. Rojahn and K. Fahr, *Ann.* **434**, 252 (1953).

⁶³⁶ K. Bowden, E. A. Braude, E. R. H. Jones, and B. C. L. Weldon, *J. Chem. Soc.* **1946**, 45.

⁶³⁷ E. G. Brain and I. L. Finar, *J. Chem. Soc.* **1958**, 2486.

⁶³⁸ E. R. H. Jones, T. Y. Shen, and M. C. Whiting, *J. Chem. Soc.* **1950**, 236.

⁶³⁹ H. Brederick, F. Effenberg, and E. H. Schweizer, *Ber.* **95**, 956 (1962).

⁶⁴⁰ I. L. Finar and K. Utting, *J. Chem. Soc.* **1959**, 4015.

⁶⁴¹ J. Marx and L. Marx-Moll, *Ber.* **87**, 1499 (1954).

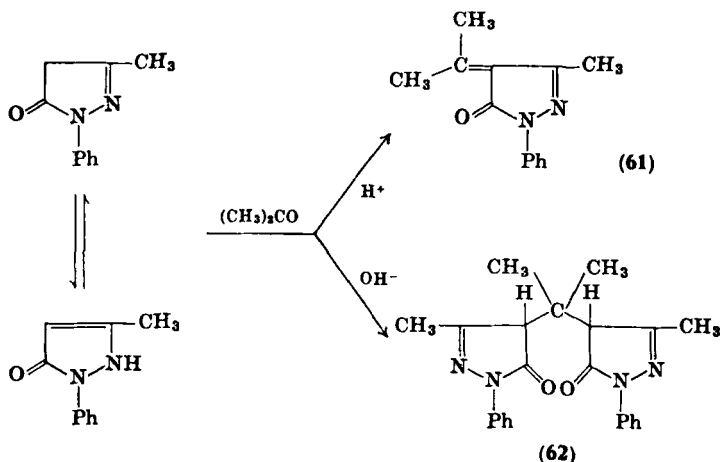
⁶⁴² C. Caradonna and M. L. Stein, *Ann. Chim. (Rome)*, **54**, 539 (1964).

⁶⁴³ E. Wahlberg, *Arkiv Kemi* **17**, 83 (1961).

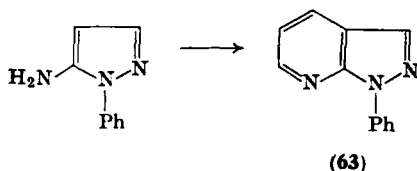
For a discussion of free radical phenylation of 1-phenyl pyrazole by benzoyl peroxide, see Lynch *et al.*^{643a}

12. Condensation with Carbonyl Groups

The hydrogen atom at the 4-position is sufficiently activated for 5-hydroxypyrazoles (pyrazolin-5-ones) to undergo condensation with ketones in acid media to yield 4-alkylidenepyrazolin-5-ones (**61**); in alkali, dipyrazolinonylmethane (**62**) derivatives are formed.^{644, 645}



The Skraup reaction can be carried out with 3-, 4-, or 5-amino-pyrazoles giving pyrazolopyridines (**63**).^{260, 646}



Such condensations are most easily performed with 3- and 5-amino-pyrazoles, as the activity of the 4-position then aids the reaction.

^{643a} M. A. Khan and B. M. Lynch, *Canad. J. Chem.* **41**, 2086 (1963).

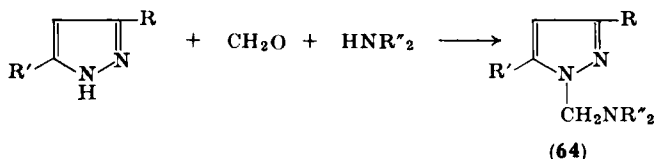
⁶⁴⁴ A. E. Porai-Koshits and M. S. Dinaburg, *Zh. Obshch. Khim.* **24**, 635 (1954).

⁶⁴⁵ M. Ridi and S. Checchi, *Gazz. Chim. Ital.* **83**, 36 (1953).

⁶⁴⁶ I. I. Grandberg, *Zh. Obshch. Khim.* **31**, 2311 (1961).

β -Dicarbonyl compounds also yield corresponding pyrazolopyridines.^{621, 647-652}

The hydrogen atom of the imino group of pyrazoles is sufficiently active to take part in Mannich reactions. Thus, pyrazoles unsubstituted on nitrogen, with formaldehyde and secondary amines, react smoothly to give high yields of dialkylaminomethyl derivatives (64) which are acid labile.⁶⁵³⁻⁶⁵⁵ Pyrazoles substituted on nitrogen give



4-hydroxymethyl derivatives with formaldehyde in acid media, but do not undergo the Mannich reaction at this 4-position.⁶⁵⁶

In neutral and alkaline media, pyrazoles unsubstituted in the 1-position undergo hydroxymethylation at that position.^{653, 657} Polymeric material of unknown structure is obtained in acid media, but from 3,5-dimethylpyrazole a small yield of 1,4-bis(hydroxymethyl)-3,5-dimethylpyrazole was isolated.⁶⁵³ Hydroxymethylation was used in the synthesis of the naturally occurring pyrazolyl-alanine.⁶⁵⁷ When the reaction is carried out in hydrochloric acid on 1-phenylpyrazole,³⁵⁰ 1,1',5,5'-tetraphenyl-3,3'-dipyrazolyl,²¹⁹ and other N-substituted pyrazoles,⁶⁵⁶ it is found that N-alkylpyrazoles give hydroxymethyl, and N-arylpyrazoles chloromethyl derivatives. The 4-position is always the site of substitution. A side reaction is the linking of pyrazoles by methylene bridges.⁶⁵⁶

⁶⁴⁷ S. Checchi, *Gazz. Chim. Ital.* **88**, 591 (1958).

⁶⁴⁸ P. Papini, *Gazz. Chim. Ital.* **83**, 861 (1953).

⁶⁴⁹ S. Checchi, P. Papini, and M. Ridi, *Gazz. Chim. Ital.* **86**, 631 (1956).

⁶⁵⁰ T. Sato, *J. Org. Chem.* **24**, 963 (1959).

⁶⁵¹ S. Checchi and M. Ridi, *Gazz. Chim. Ital.* **90**, 1093 (1960).

⁶⁵² M. Ridi, P. Papini, and S. Checchi, *Gazz. Chim. Ital.* **91**, 973 (1961).

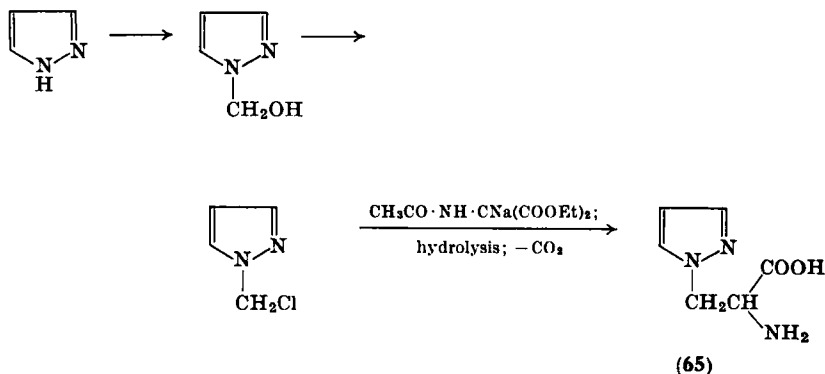
⁶⁵³ I. Dvoretzky and J. H. Richter, *J. Org. Chem.* **15**, 1285 (1950).

⁶⁵⁴ R. Hüttel and P. Jochum, *Ber.* **85**, 820 (1952).

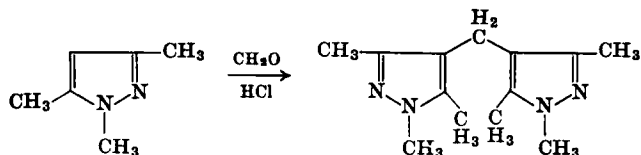
⁶⁵⁵ G. B. Bachman and L. V. Heisey, *J. Am. Chem. Soc.* **68**, 2496 (1946).

⁶⁵⁶ I. I. Grandberg, L. G. Vasina, and A. N. Kost, *Zh. Obshch. Khim.* **30**, 3324 (1960).

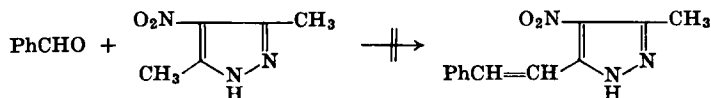
⁶⁵⁷ I. L. Finar and K. Utting, *J. Chem. Soc.* **1960**, 5272.



Musante⁶⁵⁸ was unable to condense benzaldehyde with the methyl group of 4-nitro-3,5-dimethylpyrazole. Evidently the methyl hydrogen atoms are insufficiently activated in spite of the presence of the



nitro group. Checchi was unable to condense acetylacetone with 1,3-diphenyl-4-methyl-5-aminopyrazole.⁶²¹ (On reactions of aminopyrazoles see references 658a-658c.)



In quaternized pyrazoles, 5-methyl groups are more active; thus Wizinger prepared a whole series of styryl derivatives.⁶⁵⁹ The side chain chlorination of methylpyrazoles mentioned above belongs to this group of reactions.⁵⁴⁴

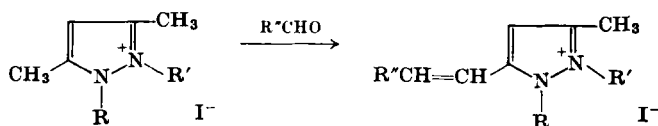
⁶⁵⁸ A. Quilico and C. Musante, *Gazz. Chim. Ital.* **72**, 399 (1942).

^{658a} S. V. Tabak, I. I. Grandberg, and A. N. Kost, *Zh. Obshch. Khim.* **34**, 2756 (1964).

^{658b} S. V. Tabak, I. I. Grandberg, and A. N. Kost, *Khim. geterocycl. Soedyn.* **1**, 116 (1965).

^{658c} I. I. Grandberg and S. V. Tabak, *Khim. geterocycl. Soedyn.* **1**, 112 (1965).

⁶⁵⁹ R. Wizinger, U.S. Patent 2,671,783 (1954); *Chem. Abstr.* **48**, 12596 (1954).



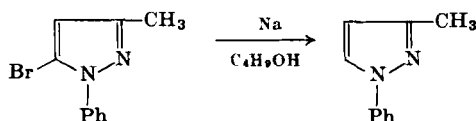
C. NUCLEOPHILIC SUBSTITUTIONS

Nucleophilic substitutions in the pyrazole series have been much less studied than electrophilic substitutions.

1. Replacement of Halogen Atoms

Halogens attached to the pyrazole nucleus are exceptionally inert, probably more so than phenyl halides, and do not undergo replacement under the usual conditions; see, for example, Michaelis and Brust.⁶⁶⁰ Only by using hydriodic acid and red phosphorus at 140–160° have halogenopyrazoles been successfully reduced to pyrazoles.^{598, 661} It appears that this method replaces halogen by hydrogen in any position of the ring. The pyrazole ring, phenyl substituents, and other functional groups are unaffected by the reduction.

Sodium and alcohol can only be used to remove a halogen atom from the 5-position in 1-arylpazoles; the ring is reduced to a pyrazoline during the reaction.^{550, 582, 662} The halogen may be removed from

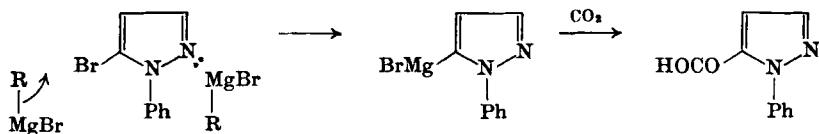


1-phenyl-4-bromo- and -4-iodo-, but not -4-chloro-pyrazole, by reduction with zinc and hydrochloric acid.⁵⁵⁰ Magnesium does not react with halogenopyrazoles under normal conditions, but in the presence of another Grignard reagent, pyrazole Grignard reagents may be obtained.⁵⁸ Halogen is most active in the 5-position, less so in the 4-, and least in the 3-position of 1-phenylpyrazole. The activity of the halide increases in the series $\text{Cl} < \text{Br} < \text{I}$, as is usual for this

⁶⁶⁰ A. Michaelis and E. Brust, *Ann.* **339**, 134 (1905).

⁶⁶¹ G. R. Clemons and T. Holmes, *J. Chem. Soc.* **1934**, 1739.

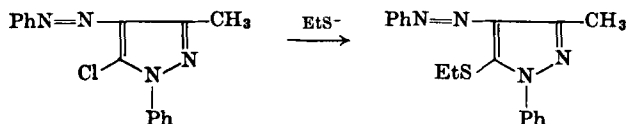
⁶⁶² R. Kitamura and S. Ishinori, *J. Pharm. Soc. Japan* **57**, 1011 (1937); *Chem. Abstr.* **32**, 2534 (1938).



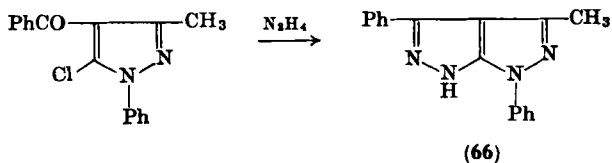
reaction.^{58, 350} The competitive reactions of mixtures of halides were studied, and the acids obtained were identified by chromatography.⁶⁶³

When the same authors studied the reaction in detail, it was found to proceed as a nucleophilic displacement on a halide atom by the R group from the accompanying reagent, which was essential for the reaction.⁵³⁴ A radical type process could not be excluded, however, as some halogen was eliminated from halogenated 1-alkylpyrazoles yielding 12–15% of dipyrazolyls.

Replacement of a halogen atom in the 5-position of a pyrazole by nucleophiles is facilitated by the presence of an electron-withdrawing substituent, such as the phenylazo group, in the 4-position, where the halogen may be replaced by amino, alkylamino, dialkylamino, arylamino, sulfhydryl, and other such groups.^{664–666}



A benzoyl group in the 4-position likewise activates a chlorine atom in the 5-position, which under comparatively mild conditions reacts with hydrazine to form pyrazolopyrazoles (e.g., **66**).^{622, 623, 667, 668} A nitro group in the 4-position has a similar activating influence on a chlorine atom in the 5-position.⁴²⁵



⁶⁶³ S. V. Tabak, I. I. Grandberg, and A. N. Kost, *Zh. Obshch. Khim.* **32**, 1562 (1962).

⁶⁶⁴ A. Michaelis, *Ann.* **338**, 267 (1904).

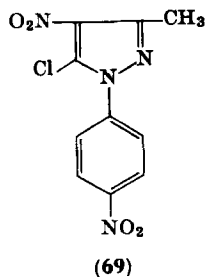
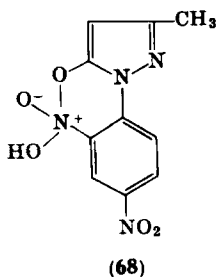
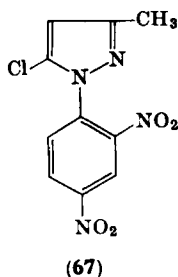
⁶⁶⁵ A. Michaelis, *Ann.* **338**, 183 (1904).

⁶⁶⁶ A. Michaelis and H. Klopstock, *Ann.* **354**, 102 (1907).

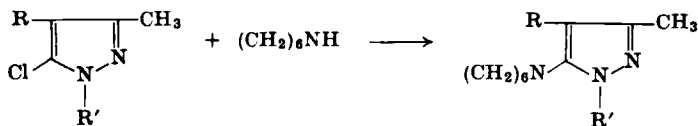
⁶⁶⁷ A. Michaelis and F. Bender, *Ber.* **36**, 523 (1903).

⁶⁶⁸ A. Michaelis, *Ann.* **361**, 251 (1908).

It is interesting to note that an electron-withdrawing group in the 4-position only activates a chlorine atom in the 5-position and not one in the 3-position.⁶⁶⁵ Rojahn suggested that the nitro groups in 1-(2',4'-dinitrophenyl)-3-methyl-5-chloropyrazole (**67**) had an unusually strong activating influence on the chlorine atom, which was easily replaced at 60–90° by hydroxyl, alkoxy, sulfhydryl, and amino groups.⁶⁶⁹ Jacobs⁴³ explained these observations by proposing the unusual intermediate cyclized form of the nitro compound (**68**). In



fact, Rojahn had obtained his pyrazole according to the method of Michaelis, published in 1900.⁶⁷⁰ Subsequently Michaelis himself reported that he had been mistaken and that the true structure of the compound included the second nitro group in the pyrazole ring, as in structure **69**, which naturally explained the high reactivity of the chlorine atom. Neither Rojahn nor Jacobs had noticed this correction. Substituents in 1-position in fact have an insignificant effect on the

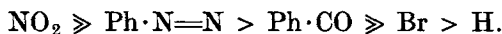


activity of halides. Rojahn and co-workers carried out a study of the kinetics of the interaction between various 1- and 4-substituted 3-methyl-5-chloropyrazoles with hexamethylenimine in absolute xylene, and showed that substituents on the nitrogen atom had no substantial influence on the rate constants of the reactions. The

⁶⁶⁹ C. A. Rojahn and H. Fegeler, *Ber.* **63B**, 2510 (1930).

⁶⁷⁰ A. Michaelis and H. Behn, *Ber.* **33**, 2596 (1900).

influence of substituents in the 4-position was quite large and can be represented by the following order:



When $\text{R} = \text{H}$ and $\text{R}' = p\text{-nitrophenyl}$, the substances do not react noticeably in 124 hours at 20° . When $\text{R} = \text{NO}_2$ and $\text{R}' = p\text{-nitrophenyl}$, at 20° the reaction rate constant is 1.7×10^{-4} . When $\text{R} = \text{Ph} \cdot \text{N}=\text{N}$ and $\text{R}' = \text{phenyl}$, the rate constant reaches 1.3×10^{-4} only at 110° ; the energy of activation is 14.5 kcal/mole.⁶⁷¹

In quaternary pyrazole salts, halogen substituents are noticeably activated; the positive charge being spread over the whole ring naturally facilitates nucleophilic attack and hence increases the lability of the halogen.⁶⁷² Concerning quaternary salts of aminopyrazoles, see Kudryashova.^{673, 674}

The halogen atom of quaternary salts of 3- and 5-halogeno-1-phenylpyrazoles may be replaced easily at $80\text{--}100^\circ$ by hydroxyl, alkoxy, sulfhydryl, thioalkyl, amino, alkylamino, dialkylamino, arylamino, or cyano groups.^{565, 675-683} The chlorine atom of quaternary salts of N-substituted 5-chloropyrazoles may be replaced by bromine^{541, 550, 579, 684, 685} or by iodine^{265, 550, 662, 684-687} by heating

⁶⁷¹ L. I. Gorbacheva, "The Lability of Halogens Connected to the Pyrazole Nucleus," Candidate's Dissertation, Moscow University (1962).

⁶⁷² A. Michaelis and H. Dorn, *Ann.* **352**, 163 (1907).

⁶⁷³ N. I. Kudryashova, N. V. Khromov-Borisov, M. N. Bobrova, and T. A. Mikhailova, *Zh. Obshch. Khim.* **33**, 173 (1963).

⁶⁷⁴ N. I. Kudryashova and N. A. Zakharova, in "Lecture Summaries for a Conference on the Chemistry of Five-membered Nitrogenous Heterocyclic Compounds," p. 32. Rostov-on-Don, 1962.

⁶⁷⁵ R. Kitamura, *J. Pharm. Soc. Japan* **61**, 19 (1941); *Chem. Abstr.* **35**, 4770 (1941).

⁶⁷⁶ A. Michaelis and H. Bindewald, *Ber.* **33**, 2873 (1900).

⁶⁷⁷ A. Michaelis and E. Gunkel, *Ber.* **34**, 723 (1901).

⁶⁷⁸ A. Michaelis, *Ann.* **331**, 199 (1904).

⁶⁷⁹ A. Michaelis, *Ann.* **339**, 117 (1905).

⁶⁸⁰ E. Thielepape and O. Spreckelsen, *Ber.* **55**, 2929 (1922).

⁶⁸¹ A. Michaelis, *Ann.* **320**, 1 (1902).

⁶⁸² K. von Auwers and F. Niemeyer, *J. Prakt. Chem.* [2] **110**, 153 (1925).

⁶⁸³ F. L. Scott, D. G. O'Donovan, and J. Reilly, *J. Am. Chem. Soc.* **75**, 4053 (1953).

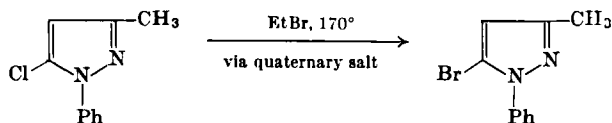
⁶⁸⁴ L. Knorr, *Ber.* **37**, 3520 (1904).

⁶⁸⁵ K. Mayer, *Ber.* **36**, 717 (1903).

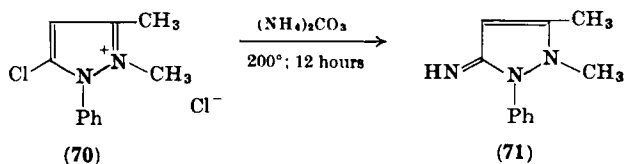
⁶⁸⁶ A. Michaelis and A. Drews, *Ann.* **350**, 321 (1906).

⁶⁸⁷ A. Michaelis, M. Kober, and W. Möller, *Ann.* **331**, 208 (1904).

the compounds at 150–170° with an excess of an appropriate alkyl halide. This type of exchange has only been studied for halogens in the 5-position; it remains uncertain whether halogens in the 4-position of quaternary pyrazole salts would be similarly activated. This



reaction has been used most of all for the synthesis of 1-phenyl-5-aminopyrazoles. Thus antipyril chloride (5-chloro-2,3-dimethyl-1-phenylpyrazolium chloride, **70**) on heating with ammonium carbonate forms 1-phenyl-2,3-dimethylpyrazolin-5-oneimine (**71**).^{677, 688} In this

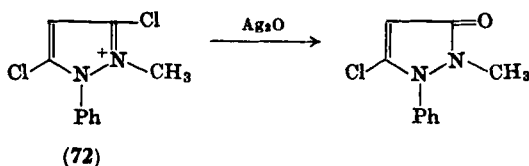


reaction primary and secondary aliphatic, aromatic, and mixed aromatic-aliphatic amines have been used^{679, 688, 689}; bromine is always more labile than chlorine.⁶⁶⁶ Pyrazolyl halides are particularly inert⁶⁸⁸ and do not take part in this reaction unless there is an aryl group activating them. Such a reaction of quaternary salts of 1-alkylpyrazoles is unknown. Elementary chlorine is able to displace bromine or iodine from 4-bromo- and 4-iodo-pyrazoles, just as elementary bromine displaces iodine from the latter. Morgan and Ackerman⁵⁷² first observed this, although they did not investigate the course of the reaction. Later, Scott⁶⁹⁰ and Hüttel and co-workers⁵⁴⁴ studied the reaction. In the literature a number of halogen exchange reactions are recorded of which the mechanisms are unclear or the structures of the products are doubtful. Thus: reaction of the methiodide of 1-phenyl-3,5-dichloropyrazole (**72**) with silver oxide proceeds by nucleophilic attack at the 3-position; usually the 5-chloro substituent is more readily displaced in this type of compound. Similarly, there is no

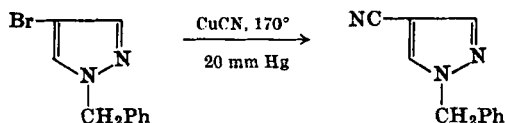
⁶⁸⁸ A. Michaelis and E. Hepner, *Ber.* **36**, 3271 (1903).

⁶⁸⁹ F. Stolz, *Ber.* **36**, 3279 (1903).

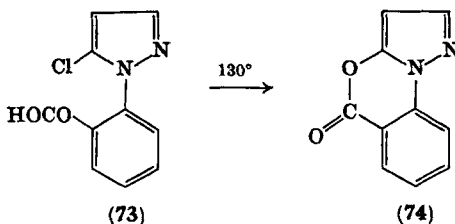
⁶⁹⁰ F. L. Scott and J. Reilly, *J. Am. Chem. Soc.* **74**, 4562 (1952).



analogy for the reaction described by Jones⁴⁵⁴ in which the bromine atom of 1-benzyl-4-bromopyrazole is replaced by cyanide on treatment with copper cyanide under exceptionally severe conditions, and it is contrary to the general view of the lability of pyrazolyl halides.

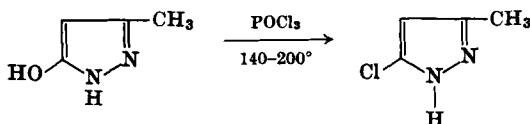


A further exception is the cyclization discovered by Michaelis,^{691, 692} in which 1-(*o*-carboxyphenyl)-5-chloropyrazole (73) on heating at 100–150° splits out hydrogen chloride and forms a pyrazolobenzoxazinone (74).



2. Replacement of a Hydroxyl Group by Halogen

The hydroxyl group of 3- and 5-hydroxypyrazoles may be replaced by halogen atoms by the action of phosphorus halides or oxyhalides or thionyl chloride.⁶⁹³ The 3-hydroxyl groups require rather more

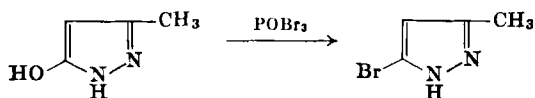


⁶⁹¹ A. Michaelis and C. Eisenschmidt, *Ber.* **37**, 2228 (1904).

⁶⁹² A. Michaelis, *Ann.* **373**, 129 (1910).

severe conditions than 5-hydroxyl groups. For the synthesis of various 3- and 5-chloropyrazoles by this method, see Michaelis and others.^{537, 545, 549-551, 565, 583, 662, 664, 674, 675, 685, 686, 691-701}

4-Hydroxyl groups may be replaced by chlorine on treatment with phosphorus oxychloride, but only if some activating group is present—at least a 1-phenyl group.⁷⁰² 3- and 5-Hydroxypyrazoles (pyrazolines) yield the corresponding bromo compounds on heating with phosphorus oxybromide at 140–200°;⁵⁶⁵ phosphorus tribromide always gives poorer results. More severe conditions are required



(about 200°) to convert pyrazolin-3-ones to 3-bromopyrazoles.⁵⁵¹ Sometimes 4-bromination occurs simultaneously as a side reaction.⁵⁵⁰

3. Metallation of Pyrazoles

Snyder⁷⁰³ was the first to obtain an organo-lithium derivative of pyrazole, when he treated 1-phenyl-3-methylpyrazole with butyllithium and then carbon dioxide, and isolated 1-phenyl-3-methylpyrazole-5-carboxylic acid. Subsequently, Alley⁷⁰⁴ showed that 1-phenyl- and 1-methyl-pyrazoles are also metallated in the 5-position by the treatment with organo-lithium compounds. Hüttell and Schön⁷⁰⁵ studied the pyrazolyl lithium derivatives in detail, and showed that in pyrazole itself the 3- and 5-hydrogen atoms were more

⁶⁹³ A. N. Kost, R. S. Sagitullin, and Y.-S. Sun, *Zh. Obshch. Khim.* **31**, 3280 (1961).

⁶⁹⁴ F. L. Scott, D. G. O'Donovan, M. R. Kennedy, and J. Reilly, *J. Org. Chem.* **22**, 820 (1957).

⁶⁹⁵ W. Ried and B. Schleimer, *Ann.* **626**, 98 (1959).

⁶⁹⁶ A. Michaelis and E. Kirstein, *Ber.* **46**, 3603 (1913).

⁶⁹⁷ A. Michaelis and H. Röhmer, *Ber.* **31**, 3193 (1898).

⁶⁹⁸ A. Michaelis and H. Röhmer, *Ber.* **31**, 2907 (1898).

⁶⁹⁹ A. Michaelis and H. Röhmer, *Ber.* **31**, 3003 (1898).

⁷⁰⁰ A. Michaelis, *Ann.* **358**, 127 (1907).

⁷⁰¹ A. Michaelis and W. Willert, *Ann.* **358**, 171 (1907).

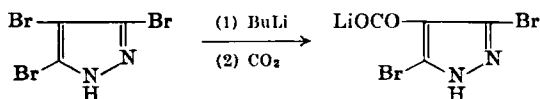
⁷⁰² L. Wolff and F. Fertig, *Ann.* **313**, 12 (1900).

⁷⁰³ H. R. Snyder, F. Verbanac, and D. B. Bright, *J. Am. Chem. Soc.* **74**, 3243 (1952).

⁷⁰⁴ P. W. Alley and D. A. Shirley, *J. Am. Chem. Soc.* **80**, 6271 (1958).

⁷⁰⁵ R. Hüttell and M. E. Schön, *Ann.* **625**, 55 (1959).

readily replaced (after the 1-proton) than that in the 4-position. The reaction takes place only at the 5-position of N-substituted pyrazoles. In the replacement of a halogen atom by lithium, the 4-position is most active; in general, halogens in the 3- and 5-positions are not

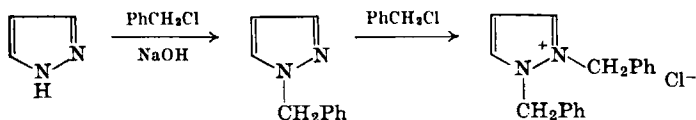


replaced. Neither can the methyl hydrogen atoms of 1,5-dimethyl-4-bromopyrazole be replaced by lithium. Phenyl-lithium reacts otherwise, in metallating at the 5-position and, similarly, in replacing the halogen atom in the 4-position.⁷⁰⁵⁻⁷⁰⁷ Concerning the action of sodamide on the pyrazole ring in an alkaline melt, see Section IV, E, 3.

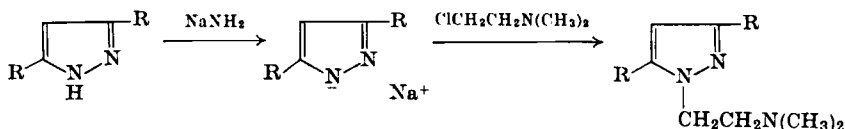
D. REACTIONS INVOLVING THE NITROGEN ATOMS

1. Alkylation and the Pyrolysis of Quaternary Salts

Alkylation of the free NH-group of pyrazoles proceeds in the usual way by the action of the normal alkylating agents. One must not forget, however, that the use of an excess of the alkylating agent can cause quaternization and the product may be difficult to isolate.



Usually a base is used in alkylation or else the sodium derivative of the pyrazole is preformed. Thus Büchi⁷⁰⁸ heated the sodium derivatives of pyrazoles with β -dimethylaminoethyl chloride and obtained good

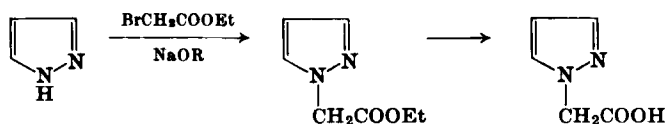


⁷⁰⁶ R. Hüttel, W. Schwarz, J. Miller, and F. Wunsch, *Ber.* **95**, 222 (1962).

⁷⁰⁷ R. Hüttel, W. Schwarz, and F. Wunsch, *Ber.* **94**, 2993 (1961).

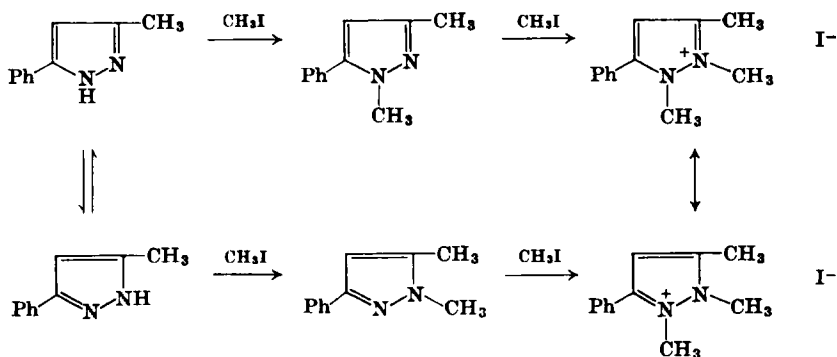
⁷⁰⁸ J. Büchi, H. R. Meyer, R. Hirt, F. Hunziker, E. Eichenberger, and R. Lieberherz, *Helv. Chim. Acta* **38**, 670 (1955).

yields of 1- β -dimethylaminoethylpyrazoles. Condensation of pyrazole with ethyl bromoacetate and subsequent hydrolysis gives pyrazolyl-1-acetic acid.⁷⁰⁹ By the action of ethyl chloroacetate and ethyl β -iodo-



propionate on 3-methyl-5-chloropyrazole, the corresponding 1-acetic and 1-propionic acids were synthesized.⁷¹⁰ As a result of many studies, principally of von Auwers and co-workers, on the alkylation of various pyrazoles and the pyrolysis of their quaternary salts, it has been possible to make generalizations concerning alkylation and the tautomeric conversions in the pyrazole series.^{60, 81, 83, 85, 152, 153, 280, 281, 463, 574, 709, 711-713}

Unsymmetrical pyrazoles can exist in two tautomeric forms, which on complete alkylation give the same methiodide.



In the above scheme the substitution of the hydrogen atom is represented as a direct process, but the mechanism has not been determined, and it is possible that either the nitrogen atom bearing

⁷⁰⁹ R. G. Jones, M. J. Mann, and K. C. McLaughlin, *J. Org. Chem.* **19**, 1428 (1954).

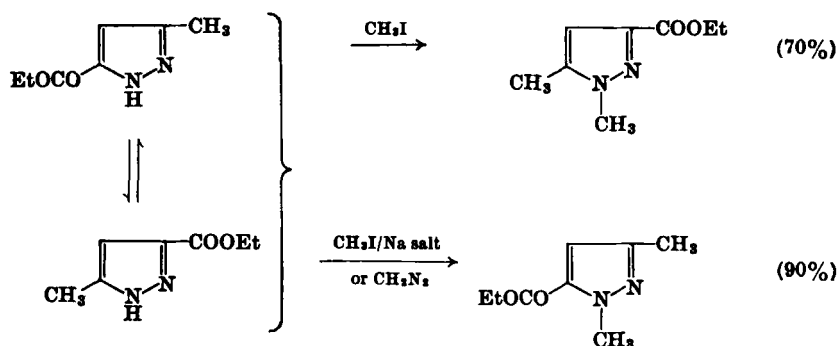
⁷¹⁰ A. Michaelis and O. Schmidt, *Ber.* **43**, 2119 (1910).

⁷¹¹ K. von Auwers and H. Broche, *Ber.* **55**, 3880 (1922).

⁷¹² K. von Auwers and H. Mauss, *J. Prakt. Chem.* [2] **110**, 204 (1925).

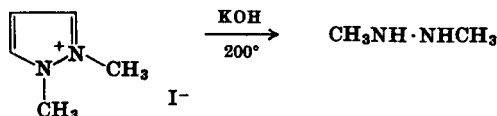
⁷¹³ K. von Auwers and C. Mausolf, *Ber.* **60**, 1730 (1927).

the hydrogen is quaternized as shown, or else the other nitrogen is attacked. Possibly this depends on the reaction conditions (e.g., whether the free pyrazole, or its anion, is the main reactant). In any case, alkylation of the tautomeric mixture formed by ethyl 3-methylpyrazole-5-carboxylate gives a preponderance of either possible isomer depending on the alkylating agent used.^{81, 86}



When the pyrazole is substituted by an electron-withdrawing group in the 3- or 5-position, alkylation usually proceeds on the nitrogen atom nearer to the electron acceptor, although a number of exceptions to this rule are known.^{83, 86} With different substituents in the 3- and 5-positions, one of the two tautomeric forms may be expected to predominate. A separation of the isomeric alkylation products is usually quite laborious. Differences in steric hindrance⁶⁸² or basicity⁷¹⁴ have been used, and also fractional crystallization of salts or distillation.⁵⁶³

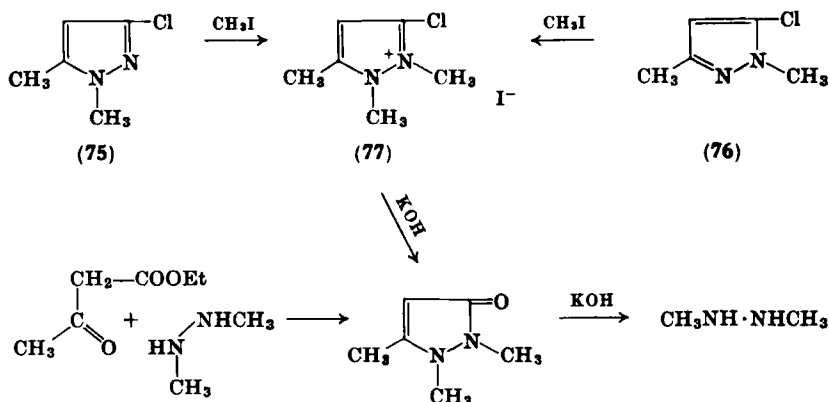
It has been proved conclusively that quaternization of N-substituted pyrazoles occurs at the 2-position (rather than at the 1-position), since alkali fusion of the methiodide of 1-methylpyrazole gives symmetrical dimethylhydrazine.⁷¹⁵ This also explains the formation of



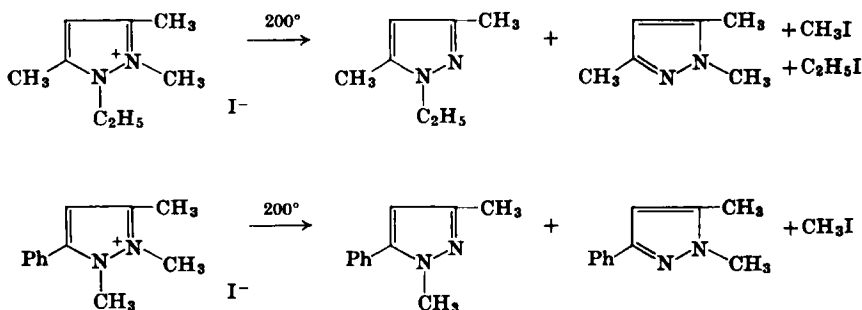
⁷¹⁴ K. von Auwers and W. Pfuhe, *Ber.* **58**, 1360 (1925).

⁷¹⁵ T. Zincke and O. Kegel, *Ber.* **22**, 1479 (1889).

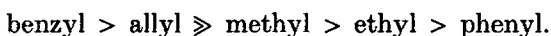
the same methiodide (77) from two isomeric dimethylchloropyrazoles (75 and 76).^{81,563}



Pyrolysis of the quaternary salts of pyrazoles causes loss of alkyl halide and reformation of N-substituted pyrazoles. If the substituents in the 3- and 5-positions are similar in character, as well as those on the two nitrogen atoms, then the two possible products will be formed in comparable quantities.^{81,83, 152, 412, 711}



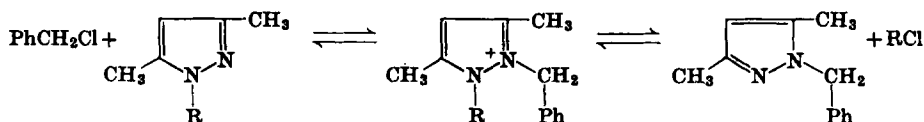
The ease with which various groups are cleaved from nitrogen diminishes in the following series:



It seems to us that this order is easily explained by the usual electronic considerations. Since the cleavage of a group from a quaternary salt involves (S_N1 or S_N2) heterolytic fission of the σ -bond linking the group to the nitrogen atom, those radicals will be cleaved most easily

which most readily form cations. Benzyl or allyl cations are stabilized by participation of the π -electrons of the benzene ring or the double bond, whereas the phenyl-nitrogen link is the strongest of all, due to π -electron conjugation, besides the ordinary σ -bond.

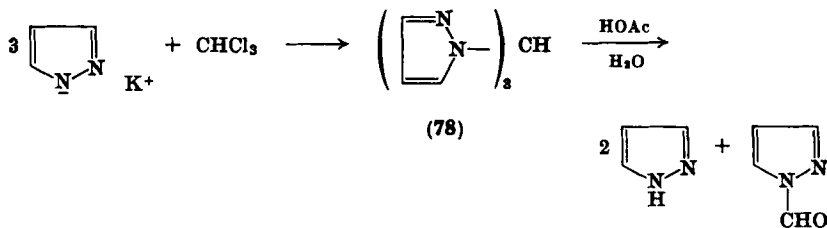
Recently transalkylation of pyrazoles was demonstrated by Grandberg and Kost.⁶²⁶ On heating with benzyl chloride in an open vessel at 150°, 1-methyl-, 1-ethyl-, and 1-propyl-3,5-dimethylpyrazole replaced the 1-alkyl by a benzyl group. Both decompositions



of the quaternary salts were reversible, but as the more volatile halide was removed from the reaction mixture, so 1-benzyl-3,5-dimethylpyrazole accumulated.

Dealkylation of N-substituted pyrazoles is difficult to accomplish and has not been studied specially. Debenzylation can be brought about by the usual methods of reduction,^{454, 705, 716, 717} or by oxidation when the pyrazole ring is stabilized by the presence of an electron-withdrawing substituent.

When 1-(2,4-dinitrophenyl)pyrazole is heated with aqueous alkali, the C—N link is cleaved by a nucleophilic displacement with the formation of pyrazole and the sodium salt of 2,4-dinitrophenol.⁷¹⁸ The carbon-nitrogen link is also cleaved readily when more than one pyrazolyl group is joined via nitrogen to the same carbon atom. Thus tri-1-pyrazolylmethane (78) on heating with aqueous acetic acid decomposes to pyrazole and 1-formylpyrazole.⁷¹⁹



⁷¹⁶ L. Birkofer, *Ber.* **75**, 429 (1942).

⁷¹⁷ V. du Vigneaud and O. K. Behrens, *J. Biol. Chem.* **117**, 27 (1937).

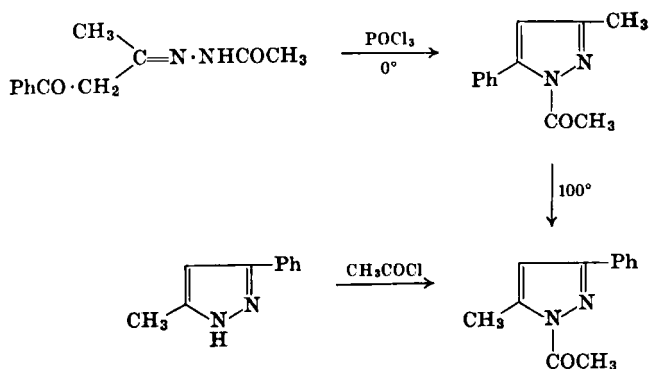
⁷¹⁸ H. R. Crocker and R. H. Hall, *J. Chem. Soc.* **1955**, 4489.

⁷¹⁹ W. Hüchel and H. Bretschneider, *Ber.* **70B**, 2024 (1937).

The synthesis of tripyrazolymethane and similar reactions of *N*-magnesium bromide derivatives of pyrazoles (see below) show that the reactive center cannot be transferred from nitrogen to the α -position of the ring as with pyrrole.⁷¹⁹⁻⁷²² Unlike the CH-group of triphenylmethane, that in tri-1-pyrazolymethane is not labile.⁷¹⁹ The 1-pyrazolyl group is presumably a weaker electron acceptor than a phenyl group because the electron pair of the 1-nitrogen atom is not completely withdrawn into the aromatic system.

2. Acylation and Isomerization of *N*-Acyl Derivatives

Although the NH-group of pyrazoles is only weakly basic it may be acylated readily by the usual agents. Acyl chlorides and anhydrides of aliphatic,^{153, 210} aromatic,⁷¹⁹ and heterocyclic⁷²³ acids, chloroformic esters,⁴⁶² phosgene,^{721, 722} and other agents^{512, 723a} give the corresponding 1-acyl derivatives. Acylation of unsymmetrical pyrazoles was studied in detail by von Auwers and his co-workers.^{83, 85, 86, 153, 156, 160, 265, 280, 281, 700, 712} Unlike alkylation (see above), acylation usually



gives the more stable isomer as the sole product. However, the 3-chloro-5-phenylpyrazole tautomer mixture reacts with acetyl chloride or *p*-nitrobenzoyl chloride to yield mixtures of isomeric products.⁷¹² The less stable isomer is rearranged to the more stable one on heating.

⁷²⁰ Q. Mingoia, *Gazz. Chim. Ital.* **61**, 449 (1931).

⁷²¹ Q. Mingoia, *Gazz. Chim. Ital.* **63**, 242 (1933).

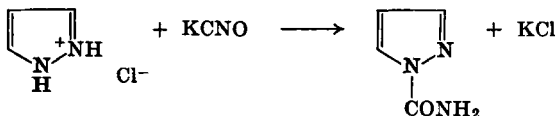
⁷²² Q. Mingoia and F. Ingrassia, *Gazz. Chim. Ital.* **64**, 279 (1934).

⁷²³ H. H. Fox and J. T. Gibas, *J. Org. Chem.* **20**, 60 (1955).

^{723a} E. Grigat and R. Pütter, *Ber.* **97**, 3027 (1964).

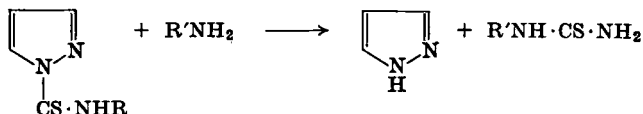
It should be noted that the structures assigned by von Auwers to these acylpyrazoles are not strictly proved. His attempts to confirm structure by a comparison of molecular refractions¹⁵⁶ are scarcely conclusive, as often the exaltations of a pair of isomers are practically the same.¹⁵³ The isomerism of acyl derivatives was considered in detail by von Auwers,^{83, 86, 156, 281} but the data often seem quite contradictory.

The isomeric conversions of *N*-carbamido derivatives are similar, and are described in the above-mentioned papers as well as in other publications^{76, 183, 184, 469, 724-726}; the *N*-carbamido derivatives are obtained by direct acylation brought about by the action of potassium cyanate on the hydrochlorides of pyrazoles.¹⁸³



Syntheses of pyrazoles with heterocyclic substituents in the 1-position via 1-thiocarbamidopyrazoles are described by Losse.⁷²⁷

N-Acylpyrazoles are even weaker bases than the parent pyrazoles: they form picrates and perchlorates,^{217, 218, 720} but do not dissolve in dilute acids. As mentioned above, the 1-acyl groups are quite labile. Transacylation by aminolysis is readily accomplished by treating various *N*-acylpyrazoles with strong amines.^{683, 695, 728}



Scott and co-workers⁷²⁹ reported a reaction between 1-amidinio-3,5-dimethylpyrazole nitrate and hydrazine. They formulated the reaction with ring opening by hydrazine attack, followed by reclosure

⁷²⁴ K. von Auwers and H. Ludewig, *Ber.* **69**, 2347 (1936).

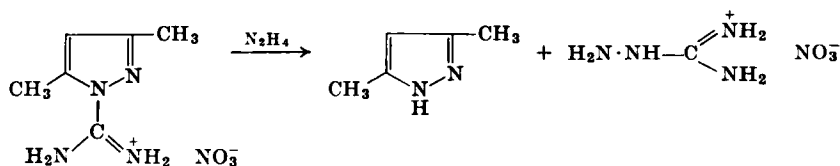
⁷²⁵ K. von Auwers, W. Buschmann, and R. Heidenreich, *Ann.* **435**, 277 (1923).

⁷²⁶ K. von Auwers, L. Fehr, V. Sass, and W. Wittekindt, *Ann.* **444**, 195 (1925).

⁷²⁷ G. Losse, A. Barth, and R. Sachadae, *Ber.* **94**, 467 (1961).

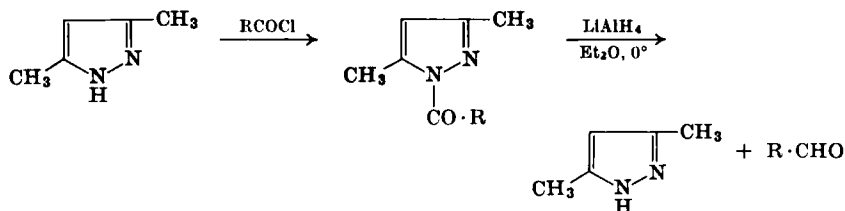
⁷²⁸ F. L. Scott, A. Ahearne, and J. Reilly, *J. Org. Chem.* **22**, 1688 (1957).

⁷²⁹ F. L. Scott, M. T. Kennedy, and J. Reilly, *Nature* **169**, 72 (1952).

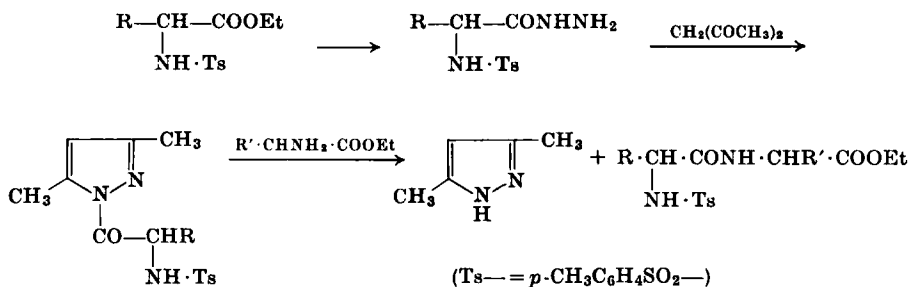


with the elimination of aminoguanidine, whereas it probably occurs by transacylation to the stronger base hydrazine.

The *N*-acyl group is easily removed in weakly acidic or basic media, especially from those 1-acylpyrazoles with electron-withdrawing substituents. The kinetics of hydrolysis and aminolysis of variously substituted acylpyrazoles was studied in great detail by Hüttel,¹⁰² using ultraviolet spectroscopy. Rate constants were found for both reactions, and an attempt was made to apply Hammett's equation to substituted pyrazoles.



When lithium aluminum hydride reacts with *N*-acylpyrazoles, the CN bond is hydrogenolyzed and aldehydes are produced in good yield. Ried even recommends this as a method of preparing otherwise inaccessible aldehydes.^{730, 731} Certain labile α -amino aldehydes were



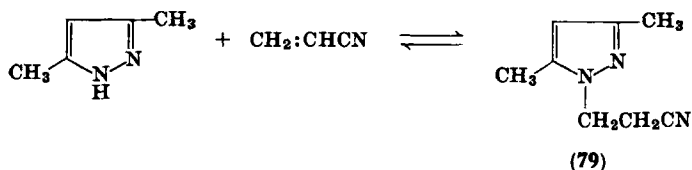
⁷³⁰ W. Ried and F. J. Königstein, *Angew. Chem.* **70**, 165 (1958).

⁷³¹ W. Ried and F. J. Königstein, *Ber.* **92**, 2532 (1959).

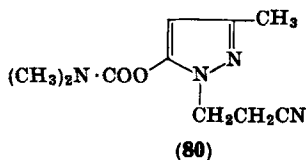
thus prepared as their acyl derivatives.⁷³² Pyrazole derivatives of α -amino acids may be used in peptide synthesis.⁷³³⁻⁷³⁵

3. The Addition of the NH-Group of Pyrazoles to Activated Double Bonds

Pyrazoles undergo Michael addition to α,β -unsaturated acids and esters,^{618, 736, 737, 737a} acrylonitrile,^{104, 483, 738} maleic anhydride, acetylene dicarboxylic ester,^{282, 737} α,β -unsaturated ketones,⁷³⁶ and quinones.¹⁰⁴ Alkaline catalysts⁶⁶⁷ are not essential in this reaction,¹⁰⁴ at least for addition to unsaturated nitriles, maleic anhydride, and quinones. The reaction is reversible, and *N*-pyrazolyl propionic



acid (79) and its derivatives cleave to acrylic acid and its derivatives.^{104, 637, 710, 739} The pyrazole (80) is active as a systemic insecticide.⁷⁴⁰



E. OTHER REACTIONS OF PYRAZOLES

1. Reduction

Pyrazole is particularly resistant to reduction; hydrogen over finely divided nickel even at 150° and 100 atmospheres pressure does not

⁷³² W. Ried and P. Pfaender, *Ann.* **640**, 111 (1961).

⁷³³ W. Ried and B. Schleimer, *Ann.* **619**, 43 (1958).

⁷³⁴ W. Ried and A. Czack, *Ann.* **642**, 133 (1961).

⁷³⁵ W. Ried and K. Marquard, *Ann.* **642**, 141 (1961).

⁷³⁶ R. H. Wiley, N. R. Smith, D. M. Johnson, and J. Moffat, *J. Am. Chem. Soc.* **77**, 2572 (1955).

⁷³⁷ R. M. Acheson and P. W. Poulter, *J. Chem. Soc.* **1960**, 2138.

^{737a} H. Reimlinger and J. Oth, *Ber.* **97**, 331 (1964).

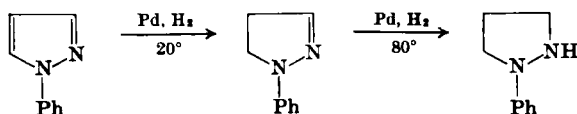
⁷³⁸ I. I. Grandberg and A. N. Kost, *Zh. Obshch. Khim.* **31**, 3700 (1961).

⁷³⁹ A. Michaelis and O. Schmidt, *Ber.* **43**, 2117 (1910).

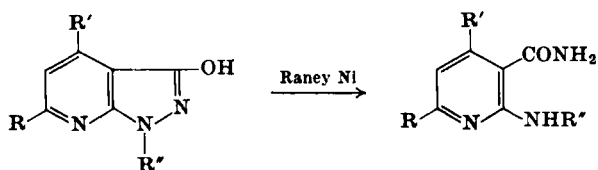
⁷⁴⁰ A. N. Kost and R. S. Sagitullin, *Zh. Obshch. Khim.* **33**, 867 (1963).

affect the ring.⁵⁴³ Those pyrazoles without phenyl substituents are especially stable.

Thoms and Schnupp⁷⁴¹ reduced pyrazole itself to pyrazoline, with a palladium catalyst in acetic acid at 20° but this is the only reported catalytic reduction of a pyrazole ring unsubstituted on nitrogen. Under these conditions *N*-phenylpyrazoles are converted to *N*-phenylpyrazolines and then at 80° to *N*-phenylpyrazolidines.⁷⁴¹



When the pyrazole ring forms part of a condensed structure and has a 3-hydroxyl group (or tautomer), the N—N link may be hydrogenolyzed comparatively smoothly by boiling an alcoholic solution of the compounds with Raney nickel.^{742, 743}



Rosenmund reduction of pyrazole acid chlorides to aldehydes never causes reduction of the ring.^{634, 635, 744, 745} Attempts to prepare the aldehydes by the sodium amalgam reduction of the anilides, however, gave only traces of the required products,⁶³⁵ but the fate of the pyrazole ring is not recorded. It is the authors' experience that pyrazoles unsubstituted on nitrogen are usually unaffected by sodium and alcohol, although the reduction to pyrazoline by sodium and alcohol at 130° and 20 atmospheres pressure has been patented.⁷⁴⁶ Reduction of *N*-phenylpyrazoles is somewhat easier: sodium and alcohol reduce them to *N*-phenylpyrazolines,^{77, 78, 207, 235, 447, 567,}

⁷⁴¹ H. Thoms and S. Schnupp, *Ann.* **434**, 305 (1923).

⁷⁴² E. C. Taylor and K. S. Hartke, *J. Am. Chem. Soc.* **81**, 2456 (1959).

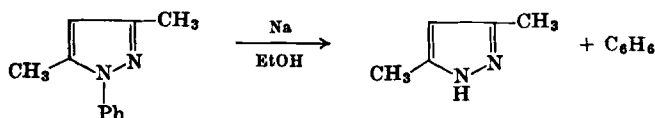
⁷⁴³ E. C. Taylor and J. W. Barton, *J. Am. Chem. Soc.* **81**, 2448 (1959).

⁷⁴⁴ C. A. Rojahn and H. E. Kühling, *Arch. Pharm.* **264**, 337 (1926).

⁷⁴⁵ K. W. Rosenmund, *Ber.* **51**, 585 (1918).

⁷⁴⁶ H. Bohme, German Patent 703,844 (1930); *Chem. Zentr.* **II**, 2512 (1931).

⁷⁴⁷⁻⁷⁵⁵ but sometimes the reaction is complicated.⁷⁵⁶⁻⁷⁶⁰ Thus, Marchetti records the formation of 3,5-dimethylpyrazole in the reduction of the 1-phenyl derivative.⁷⁶¹ By reduction of the methiodide



of 1,3,5-trimethylpyrazole with sodium and alcohol, Knorr⁷⁶² isolated a compound (mp 109–110°) which does not give the reactions characteristic of pyrazolines, and whose structure was not established. The pyrazole ring is stable to lithium aluminum hydride⁴⁵⁴ and hydrazine hydrate in the presence of palladium^{198, 260} or nickel.⁷⁴ There are many papers on the reduction of pyrazole compounds with hydriodic acid (for example Michaelis⁵⁹⁸ and Clemo⁶⁶¹), amalgamated zinc and hydrochloric acid (Michaelis⁵⁵⁰ and Finar⁶²⁰), stannous chloride (Kosuge³⁴²), and tin in hydrochloric or acetic acid,^{77, 194, 527, 763} sodium sulfide,^{241, 249, 587} and aluminum amalgam.⁵⁸⁸ In all these reductions the pyrazole ring remains unaffected.

2. Oxidation

The pyrazole ring is stable to oxidation, and side chains attached to it may be oxidized to carboxylic acids. Thus various alkylpyrazoles

⁷⁴⁷ L. C. Reiford and W. I. Peterson, *J. Org. Chem.* **1**, 544 (1937).

⁷⁴⁸ L. Knorr and E. Jochheim, *Ber.* **36**, 1275 (1903).

⁷⁴⁹ L. Knorr, *Ber.* **28**, 706 (1895).

⁷⁵⁰ L. Knorr and P. Duden, *Ber.* **26**, 103 (1893).

⁷⁵¹ F. Ach, *Ann.* **253**, 44 (1889).

⁷⁵² K. von Auwers and F. Dersch, *Ann.* **462**, 104 (1928).

⁷⁵³ L. Panizzi and E. Monti, *Gazz. Chim. Ital.* **77**, 556 (1947).

⁷⁵⁴ A. Michaelis, *Ann.* **331**, 221 (1904).

⁷⁵⁵ L. Balbiano, *Gazz. Chim. Ital.* **19**, 689 (1889).

⁷⁵⁶ K. von Auwers, *Ber.* **65**, 833 (1932).

⁷⁵⁷ L. Balbiano, *Gazz. Chim. Ital.* **18**, 354 (1888).

⁷⁵⁸ G. Marchetti, *Atti accad. naz. Lincei*, Part I, 86 (1892); *Chem. Zentr.* **63** (part I), 699 (1892).

⁷⁵⁹ G. Marchetti, *Atti accad. naz. Lincei*, Part II, 372 (1891); *Chem. Zentr.* **63** (part I), 135 (1892).

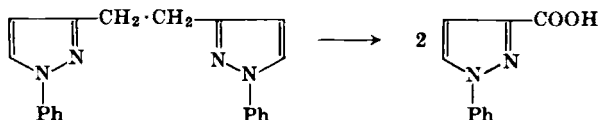
⁷⁶⁰ G. Marchetti, *Gazz. Chim. Ital.* **22**, Part II, 368 (1892).

⁷⁶¹ G. Marchetti, *Atti R. Accad. Lincei* [5], Part I, 337 (1892).

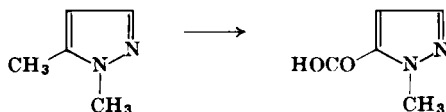
⁷⁶² L. Knorr and H. Laubman, *Ber.* **21**, 1205 (1888).

⁷⁶³ G. T. Morgan and J. Reilly, *J. Chem. Soc.* **105**, 438 (1914).

were oxidized with permanganate.^{764, 765} The oxidation proceeds best in alkaline media, for example with methyl groups,^{576, 766, 767} ethyl groups,^{576, 768, 769} and acyl groups.^{229, 350, 356, 357, 458, 480, 623, 632, 770-772} Di- and tri-carboxylic acids may be obtained from pyrazoles with more than one side chain or with a carboxyl group and other side chains.^{420, 590, 591, 767, 773-775}



Other agents have been used to oxidize pyrazole side chains, thus Michaelis⁷⁷⁶ used a chromic acid mixture, Balbiano⁷⁷⁷ and Fries,⁷⁷⁸ nitric acid. Groups in the 4-position characteristically undergo oxidation most readily. Oxidation of 1-phenyl-5-chloro-3,4-dimethylpyrazole and even the corresponding 3-methyl-4-ethyl compound commences with the substituent in the 4-position.⁷⁶⁸ Alkyl groups in the 1-position cannot normally be oxidized; thus, 1,5-dimethylpyrazole gives only 1-methylpyrazole-5-carboxylic acid.⁵⁶¹ However, 1-benzylpyrazoles with electron-withdrawing substituents in the pyrazole ring may be oxidized quite easily with permanganate. The 1-benzoylpyrazoles initially formed lose the acyl group in aqueous solution.^{58, 672}



⁷⁶⁴ E. Benary, *Ber.* **54**, 2201 (1926).

⁷⁶⁵ L. Knorr, *Ber.* **28**, 701 (1895).

⁷⁶⁶ E. Benary, *Ber.* **59**, 2198 (1926).

⁷⁶⁷ R. Stroemer and O. Martinsen, *Ann.* **352**, 335 (1907).

⁷⁶⁸ A. Michaelis, U. Voss, and M. Greiss, *Ber.* **34**, 1303 (1901).

⁷⁶⁹ E. Dyer and T. B. Johnson, *J. Am. Chem. Soc.* **56**, 222 (1934).

⁷⁷⁰ L. Wolff, *Ann.* **325**, 182 (1902).

⁷⁷¹ A. Rönneburg, *Ber.* **36**, 1128 (1903).

⁷⁷² E. Benary, *Ber.* **43**, 1067 (1910).

⁷⁷³ L. Claisen and P. Roosen, *Ber.* **24**, 1890 (1891).

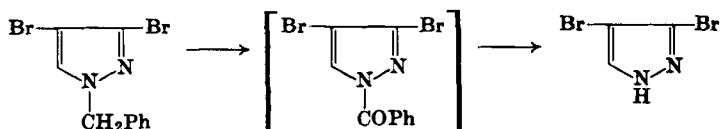
⁷⁷⁴ G. D. Rosengarten, *Ann.* **279**, 240 (1894).

⁷⁷⁵ D. S. Acker, *J. Org. Chem.* **28**, 2533 (1963).

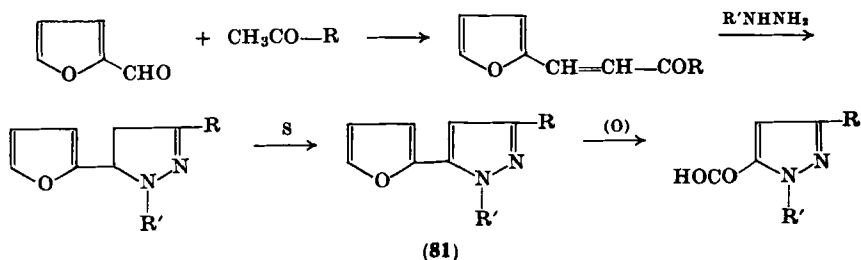
⁷⁷⁶ A. Michaelis, *Ann.* **373**, 172 (1910).

⁷⁷⁷ L. Balbiano, *Gazz. Chim. Ital.* **28**, Part I, 387 (1898).

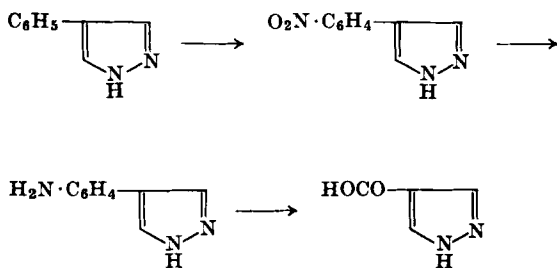
⁷⁷⁸ K. Fries, K. Fabel, and H. Eckhardt, *Ann.* **550**, 31 (1941).



A convenient and recently discovered method for synthesizing pyrazole-5-carboxylic acids involves the easy oxidation of the furan ring of 2-furylpyrazoles (81) with neutral permanganate. Only the furan ring is oxidized, and alkyl or aryl substituents are left untouched.^{106, 107} By condensing 2-acetylfuran with an aldehyde as the



first stage, the method may be used to prepare pyrazole-3-carboxylic acids. When a phenyl group is to be oxidized, it is first nitrated and the product reduced, as the aminophenyl group is more susceptible to attack.⁷⁷⁹⁻⁷⁸¹ Under severe conditions even 1-, 3-, and 5-phenyl

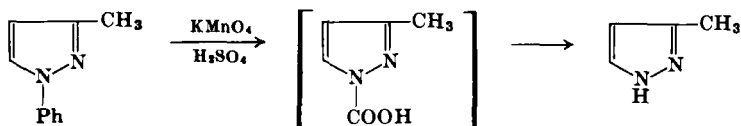


groups can be oxidized without touching the pyrazole ring.^{570, 779-781} It is curious that potassium permanganate in acid media oxidizes a

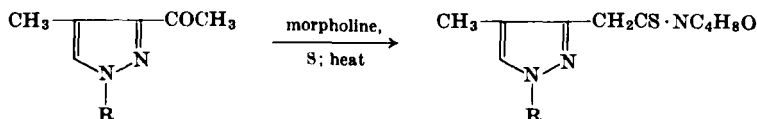
⁷⁷⁹ E. Buchner and C. Hachumian, *Ber.* **35**, 41 (1902).

⁷⁸⁰ W. Behaghel and E. Buchner, *Ber.* **35**, 34 (1902).

⁷⁸¹ E. Buchner, *Ber.* **27**, 3247 (1894).



benzene ring and yet leaves a methyl group unchanged.^{334,440} Sometimes with strongly alkaline permanganate, however, complete oxidation of pyrazoles to carbon dioxide is observed. The pyrazole nucleus is also completely destroyed by electrolytic oxidation⁶³⁰ and ozonolysis (see Section II, A). Willgerodt oxidation with sulfur and an amine proceeds normally in the pyrazole series.⁷⁸²



By oxidation of 1-phenyl-3-methyl-5-aminopyrazole, Michaelis⁷⁸³ obtained a compound which he called "acipyrazole," but its structure has not been established.

3. Examples of Alkaline Cleavage

It is known that alkaline fusion of quaternary salts of pyrazoles results in the complete cleavage of the ring to 1,2-dialkylhydrazines.^{715, 784-788} The methiodide of 1-methylpyrazole must be heated to 200° with potassium hydroxide. Alkali fusion has also been used for the cleavage of pyrazolinones; see for example Knorr⁷⁸⁷ and Pelz *et al.*⁷⁸⁹ It was recently observed that the pyrazole rings of indazole and 1-benzylindazole are cleaved by the action of sodamide.⁷⁹⁰ Such instability of the pyrazole ring to the action of very strong bases

⁷⁸² E. G. Brain and I. L. Finar, *J. Chem. Soc.* **1957**, 2356.

⁷⁸³ A. Michaelis and A. Schäfer, *Ann.* **397**, 119 (1913).

⁷⁸⁴ H. von Pechmann and K. Wehsarg, *Ber.* **21**, 2994 (1888).

⁷⁸⁵ L. Knorr and A. Köhler, *Ber.* **39**, 3257 (1906).

⁷⁸⁶ L. Knorr and H. Taufkirch, *Ber.* **25**, 771 (1892).

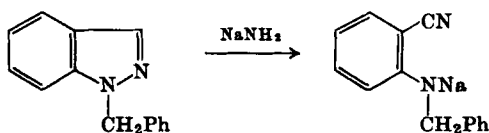
⁷⁸⁷ L. Knorr, *Ber.* **39**, 3265 (1906).

⁷⁸⁸ L. Knorr and A. Weidel, *Ber.* **42**, 3523 (1909).

⁷⁸⁹ W. Pelz, W. Püschel, H. Schellenberger, and K. Löffler, *Angew. Chem.* **72**, 967 (1960).

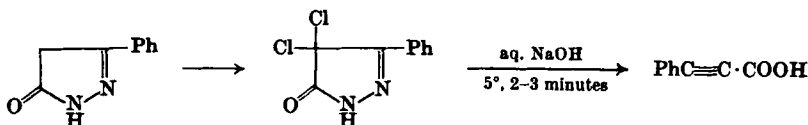
⁷⁹⁰ R. Huisgen, *Angew. Chem.* **72**, 359 (1960); A. M. Simonov, B. K. Martsokha, and F. T. Pozharskii, *Zh. Obshch. Khim.* **32**, 2388 (1962).

invites further study, on account of the analogous cleavage of isoxazoles, which occurs with great ease.⁷⁹¹ 1,3,5-Triphenylpyrazole-4-carboxylic acid survives heating at 160° with alcoholic potassium hydroxide solution.⁷⁹² Similarly, 1-phenyl-3,5-dimethyl-4-cyanopyrazole was hydrolyzed by refluxing for 40–50 hours in aqueous alcoholic potassium hydroxide solution without destruction of the pyrazole ring.⁷⁹³



4. Cleavage of the Ring on Halogenation

Carpino⁷⁹⁴ showed that dichloropyrazolinones on alkaline hydrolysis are converted to acetylenic acids. Similarly 1-substituted



pyrazolinones and acetates of hydroxypyrazolinones are ring-opened.⁷⁹⁵ Under these conditions monochloro compounds form α,β -unsaturated acids, principally of the *cis*-configuration.⁷⁹⁶

Fusco and Rossi⁷⁹⁷ observed the rupture of the pyrazole ring when 4-nitrosopyrazoles (**81**) were treated with phosphorus pentachloride, forming isomeric chlorocyanoazines (**82** and **83**). The reaction is evidently similar to the second-order Beckmann rearrangement.⁷⁹⁸

To this group of reactions may be added the conversion of pyrazolinone (**84**) to pyrazolo-oxazinone (**85**) by the action of bromine

⁷⁹¹ N. K. Kochetkov and S. D. Sokolov, *Advan. Heterocyclic Chem.* **2**, 403 (1963).

⁷⁹² O. Seidel, *J. Prakt. Chem. Ser. 2*, **58**, 153 (1898); R. Fusco and R. Juston, *Gazz. Chim. Ital.* **67**, 3 (1937).

⁷⁹³ E. Benary, *Bcr.* **60**, 1883 (1927).

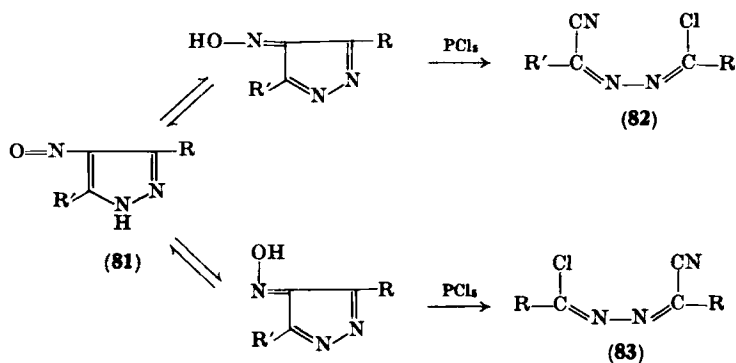
⁷⁹⁴ L. A. Carpino, *J. Am. Chem. Soc.* **80**, 599 (1958).

⁷⁹⁵ L. A. Carpino, *J. Am. Chem. Soc.* **80**, 5796 (1958).

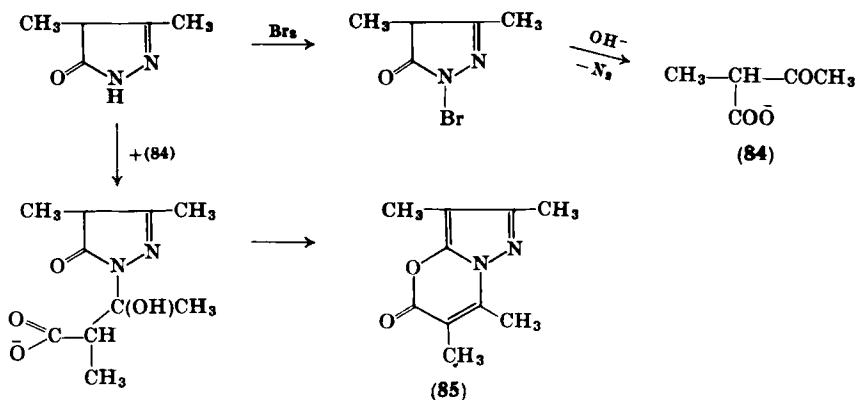
⁷⁹⁶ L. A. Carpino, *J. Am. Chem. Soc.* **80**, 601 (1958).

⁷⁹⁷ R. Fusco and S. Rossi, *Tetrahedron* **3**, 209 (1958).

⁷⁹⁸ R. T. Conley and B. E. Nowak, *J. Org. Chem.* **27**, 3196 (1962).



with subsequent hydrolysis. The formation of the second ring is brought about by the hydrolytic cleavage of one molecule of the starting pyrazolinone.⁷⁹⁹



⁷⁹⁹ R. Hüttel, H. Wagner, and H. Sickenberger, *Ann.* **607**, 109 (1957).

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Numbers in parentheses are reference numbers and indicate that an author's work is referred to although his name is not cited in the text.

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